

PATENT ABSTRACTS OF JAPAN

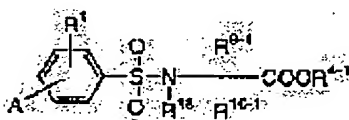
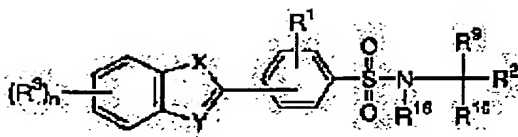
(11)Publication number : 10-204059

(43)Date of publication of application : 04.08.1998

(51)Int.Cl. C07D209/10
A61K 31/34
A61K 31/38
A61K 31/40
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C07D235/18
C07D263/56
C07D277/66
C07D307/79
C07D333/54
C07D405/12
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(21)Application number : 09-023177 (71)Applicant : ONO PHARMACEUT CO
LTD
(22)Date of filing : 22.01.1997 (72)Inventor : TAKAHASHI KANJI
SUGIURA TSUNEYUKI

(54) PHENYLSULFONAMIDE DERIVATIVE



(57)Abstract:

PROBLEM TO BE SOLVED: To obtain the subject new compound having an inhibiting action to a matrix metalloproteinase, e.g. gelatinase, stromelysin or a collagenase, and useful for the prevention and treatment of rheumatoid arthritis, etc.

SOLUTION: This phenylsulfonamide derivative is an objective compound expressed by formula I [R¹ is H or a 1-4C alkyl; R² is COOR⁴ (R⁴ is a 1-8C alkyl, phenyl, etc.), CONHOR⁵ (R⁵ is H, a substituted 1-4C alkyl, etc.); X is O, S, etc.; Y is CH or N; R³ is H, a 1-4C alkyl, etc., (n) is 1-4; R⁹, R¹⁰ are H, a 1-8C alkyl, etc.; R¹⁸ is H, a 1-4C alky or a 1-4C alkoxy carbonyl], e.g. N-[4-(2-indolyl)phenylsulfonyl-D-alanine.

Further, to obtain the objective compound, e.g. it is preferable to react a compound expressed by formula II (A is a halogen or

trifluoromethanesulfonyloxy) with a compound expressed by formula III in the presence of an organic solvent and a metal halide by using a catalyst at 0-100°C.

* NOTICES *

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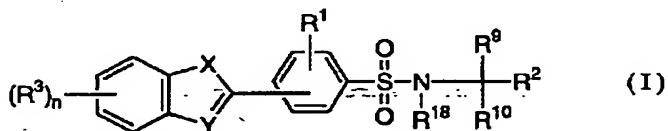
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CLAIMS

[Claim(s)]

[Claim 1] General formula (I)

[Formula 1]



(R¹ among a formula a hydrogen atom, or C1 - 4 alkyl groups) [express and] R² expresses a -COOR⁴ group or a -CONHOR⁵ group, R⁴ (1) hydrogen atom, (2) C1 - 8 alkyl group, and (3) phenyl group, Or (4) phenyl groups, a -OCOR⁶ group (R⁶ expresses C1 - 4 alkyl groups among a basis.), or a -CONR⁷R⁸ group (independently R⁷ and R⁸ among a basis, respectively) A hydrogen atom, or C1 - 4 alkyl groups is

expressed. C1 replaced by either - 4 alkyl groups are expressed, R⁵ expresses C1 replaced by the hydrogen atom, C1 - 8 alkyl groups, the phenyl group, or the phenyl group - 4 alkyl groups, X is an oxygen atom, a sulfur atom, or a -NR¹⁷ group (R¹⁷ among a basis). A hydrogen atom, C1 - 4 alkyl groups, C1 replaced by the phenyl group - 4 alkyl groups, C1 replaced by C1 - 8 alkoxycarbonyl groups, or a phenyl group - 4 alkoxycarbonyl groups are expressed. Express, Y expresses CH basis or a nitrogen atom, and R³ A hydrogen atom, C1 - 4 alkyl groups, C1 - 4 alkoxy groups, a halogen atom, A trifluoromethyl group, a hydroxyl group, a carboxyl group, C1 - 8 alkoxycarbonyl groups, A nitro group, a -NR⁷R⁸ group (R⁷ and R⁸ express the same meaning as the above among a basis.), or a -CONR⁷R⁸ group (among a basis) R⁷ and R⁸ express the same meaning as the above. Express, n expresses the integer of 1-4, and R⁹ and R¹⁰, respectively independently, (1) A hydrogen atom, (2) C1 - 8 alkyl group (however, one -CH₂-basis in an alkyl group may be changed with one sulfur atom.), a (3)-COR¹¹ group (the inside of a basis, and R¹¹ -- a hydroxyl group and C -- one to 8 alkyl group) C1 - 4 alkoxy groups, or the -NR¹⁵R¹⁶ group (independently R¹⁵ and R¹⁶ among a basis, respectively) replaced by C1 - 8 alkoxy groups, the phenoxy group, and the phenyl group C1 replaced by the hydrogen atom, C1 - 4 alkyl groups, the phenyl group, one piece, or two phenyl groups - 4 alkyl groups are expressed. It expresses. (4) ring group, (5) a heterocycle group (the ring of the above (4), or the heterocycle of the above (5) -- one to three C -- one to 4 alkyl group) it may be replaced by C1 - 4 alkoxy groups, the halogen atom, the hydroxyl group, and the trifluoromethyl group. Or C1 replaced by one basis chosen from (6) following (i) - (viii) - 8 alkyl groups, (i) A -COR¹¹ group (R¹¹ expresses the same meaning as the above among a basis.), (ii) C1 - 4 alkoxy groups, a (iii) hydroxyl group, a (iv) benzyloxy group, (v) A guanidino group, a (vi) -NR¹²R¹³ group (independently R¹² and R¹³ among a basis, respectively) A hydrogen atom, C1 - 4 alkyl groups, or a -COOR¹⁴ group (among a basis) R¹⁴ expresses C1 - 4 alkyl groups, or benzyl. It expresses. (vii) a ring group or a (viii) heterocycle group (the ring of said (vii), or the heterocycle of said (viii) -- one to three C -- one to 4 alkyl group) It may be replaced by C1 - 4 alkoxy groups, the halogen atom, the hydroxyl group, and the trifluoromethyl group. Express and R¹⁸ A hydrogen atom, C1 - 4 alkyl groups, C1 replaced by C1 - 4 alkyl groups, C1 - 8 alkoxycarbonyl groups, or the phenyl group replaced by the phenyl group - 4 alkoxycarbonyl groups are expressed. The phenyl sulfonamide derivatives shown or those nontoxic salts.

[Translation done.]

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DETAILED DESCRIPTION

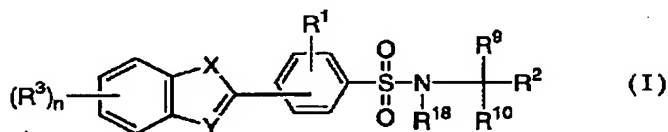
[Detailed Description of the Invention]

[0001]

[Field of the Invention] This invention relates to a phenyl sulfonamide derivative, its manufacturing method, and the drugs that contain the derivative as an active principle.

[0002] It is general formula (I) in more detail.

[Formula 2]



(all the signs express the same meaning as a postscript among a formula.) -- it is related with the phenyl sulfonamide derivatives shown, those nontoxic salts, those manufacturing methods, and the drugs containing them.

[0003]

[The background and conventional technology of an invention] Matrix metalaw proteinase (it is hereafter written as MMP.) to an active center Zinc. (it is hereafter written as Zn^{2+} .) -- it being the neutral metalaw proteinase which it has, and, It is acting on growth, organization reconstruction, etc. of a joint organization, an osseous tissue, connective tissue, etc. by decomposing collagen, a laminin, proteoglycan, fibronectin, elastin, gelatin, etc. under a physiological situation. Ten or more kinds of molecular species in which MMP will differ in the primary structure by the present are identified. Specifically Interstitial collagenase (MMP-1), leucocyte collagenase (MMP-8), The gelatinase A (MMP-2), the gelatinase B (MMP-9), the SUTOROMU lysin 1 (MMP-3), the SUTOROMU lysin 2 (MMP-10), Mathot Rira Isin (MMP-7), etc. are mentioned.

[0004] As character common to these each enzyme, it has Zn^{2+} in (1) active center, and calcium (Ca^{2+}) is needed for enzyme activity, (2) It has [it being secreted as a latent type enzyme and receiving activation out of a cell,] high homology in (3) amino acid sequences, (4) having various extracellular matrix component resolution which exists in the living body, and (5) -- it is known that activity will be checked by organization metalaw proteinases inhibitor (TIMP) which is common inhibitor etc.

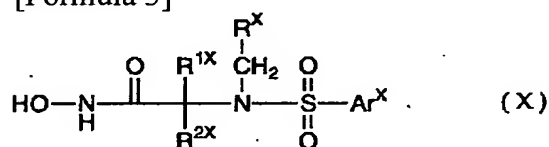
[0005] It is thought that inhibitor of MMP is useful for the prevention and/or the therapy of various diseases which are produced when secretion and activity of MMP carry out a gastric upset. For example, rheumatism, osteoarthritis, morbid osteoclastosis, osteoporosis, periodontosis, interstitial nephritis, The disease of arteriosclerosis, versicular emphysema, liver cirrhosis, cornea damage, transition permeation of a cancer cell, or growth, an autoimmune disease, the diseases (Crohn's disease, a SHUGUREN disease, etc.) by the blood vessel transmigration of the cell of a leucocyte system or permeation, the vascularization, etc. are mentioned.

[0006] Some compounds which have matrix metalaw proteinase inhibitory action are known. Especially, it is known that the substrate near the cutting point of collagen (Gly-Ile-Ala-Gly or Gly-Leu-Ala-Gly) has collagenase and high compatibility. The substrate analog matrix metalloproteinase inhibitor which has a zinc compatibility group in the cleavage site of this substrate and which performed chemical modification, Curr., [Inhibitors of matrix metalloproteinases (MMP's), Nigel RA Beeley, Phillip RJ Ansell, Andrew JP Docherty et al. currently studied. [many] Opin. Ther. Patents, 4,7-16 (1994) and Current Drugs Ltd ISSN 0962-2594 Reference]. However, since these substrate analog inhibitor is peptide analogs, it is expected that

there are various problems. For this reason, to form these inhibitor into un-peptide is desired, and some are reported.

[0007]For example, in the specification of EP No. 606046, it is general formula (X).

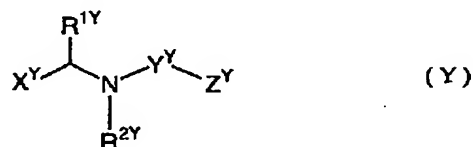
[Formula 3]



the inside of a formula, and (a) Ar^{X} -- carbocyclic or heterocyclic aryl group; R^{X} -- a hydrogen atom. ; $\text{R}^{1\text{X}}$, such as a low-grade alkyl group and carbocyclic aryl low-grade alkyl group, a hydrogen atom, Are a hydrogen atom or a low-grade alkyl group, or; or (b) R^{X} , and $\text{R}^{1\text{X}}$ become together with the chain with which they are added, and; $\text{R}^{2\text{X}}$, such as a low-grade alkyl group and carbocyclic aryl low-grade alkyl group, a 1,2,3,4-tetrahydro isoquinoline, a piperidine ring etc. -- formation; -- Ar^{X} and $\text{R}^{2\text{X}}$ having the meaning which (a) defined, or; or (c) $\text{R}^{1\text{X}}$, and $\text{R}^{2\text{X}}$ becoming together with the carbon atom in which they are added, and them, Three to C7 cycloalkane replaced by un-replacing or a low-grade alkyl group, ;, such as oxa cyclohexane and ****-cyclohexane, Ar^{X} , and $\text{R}^{2\text{X}}$ have the meaning which (a) defined. It is indicated that the aryl sulfonamide derivative shown has matrix metalaw proteinase inhibitory action.

[0008]the specification of WO No. 9535276 -- general formula (Y)

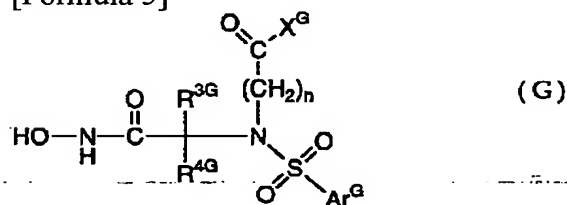
[Formula 4]



alpha-amino-acid side chain; $\text{R}^{2\text{Y}}$ of nature [Y / the inside of a formula, and / X / $^{1\text{Y}}$ / COOH group and CONHOH basis; R], or non-nature -- $\text{Z}^{1\text{Y}}\text{Q}^{\text{Y}}\text{W}^{\text{Y}}$ group; $\text{Z}^{1\text{Y}}$ -- a hydrogen atom. Aryl group etc.; (i) $\text{Q}^{\text{Y}}\text{W}^{\text{Y}}$ becomes together and A single bond, O atom, S atom, and $\text{W}^{\text{Y}}\text{Q}^{\text{Y}}$ (ii) C1 - 20 alkyl groups, etc., A single bond and $\text{W}^{\text{Y}}\text{Q}^{\text{Y}}$ (iii) C9 - 20 alkyl groups, etc., Q^{Y} (iv) A single bond, W^{Y} -- C1 - 8 alkyl-group; -- Y^{Y} -- SO_2 group; -- Z^{Y} expresses the aryl group or heteroaryl group which may be replaced arbitrarily. It is indicated that the compound shown has matrix metalaw proteinase inhibitory action.

[0009]the specification of WO No. 9627583 -- general formula (G)

[Formula 5]

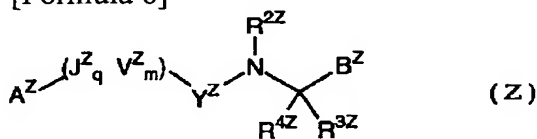


the inside of a formula, and n -- 1 - 6; X^{G} -- a hydroxyl group and C -- one to 6 alkoxy group, $\text{NR}^{1\text{G}}\text{R}^{2\text{G}}, \text{R}^{3\text{G}}$ and $\text{R}^{4\text{G}}$ A hydrogen atom, C1 - 6 alkyl groups, etc. : Ar^{G} An aryl group (C6-10), (C5-9) A heteroaryl group, an alkyl (C1-6) (C6-10) aryl group, (C1-6) An alkoxy (C6-10) aryl group, a $_2$ (alkoxy (C1-6)) (C6-10) aryl group, (C6-10) An aryloxy (C6-10) aryl group, a heteroaryloxy (C5-9) (C6-10) aryl group, (C1-6) An

alkyl (C5-9) heteroaryl group, an alkoxy (C1-6) (C5-9) heteroaryl group, (C1-6) A₂ (C5-9) heteroaryl group (alkoxy), (C6-10) An aryloxy (C5-9) heteroaryl group and a heteroaryloxy (C5-9) (C5-9) heteroaryl group are expressed. It is indicated that the compound shown has matrix metalaw proteinase inhibitory action.

[0010]On the other hand, in the specification of WO No. 9315047, it is a general formula (Z).

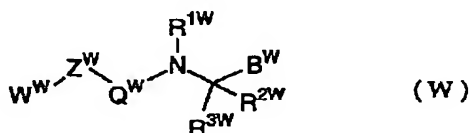
[Formula 6]



(-- the inside of a formula, and A^Z -- a) -- a -Q^Z-X^Z group (Q^Z -O-) S-, a -NR^Z-basis, a single bond, and X^Z -The aromatic ring or heterocycle of 5 and 6 members, A b)-CN basis, a -NO₂ group, a -N₃ group, a -NR^ZR^{1Z} group, -OR^Z group, a -COR^Z group, a -CO₂R^Z group (independently R^Z and R^{1Z}, respectively) ;J^Z, such as a hydrogen atom, C1 - 18 alkyl groups, C2 - 18 alkenyl groups, the alkanediyl group of C1 - 8 of bivalence, An alkanediyl group or an alkynediyl group; V^Z A phenylene group, 0 or 1; Y^Z;q, such as a francdiyl group, a thiophenediyl group, and a thiazolediyl group, and m A single bond, - A CH₂-basis, a -C(=O)-basis, a -C(=S)-basis, a -S(=O)₂-basis, or a -P(=O) (one to OC6 alkyl)-basis (however, when Y^Z is a -S(=O)₂-basis) Q^Z does not express a single bond.;R^{2Z} A hydrogen atom, C1 - 6 alkyl groups, C2 - 6 alkenyl groups, C2 - 6 alkynyl groups, -;R^{3Z}, such as CO (one to C6 alkyl) basis and a -CO₂ (one to C6 alkyl) basis, and R^{4Z}, respectively independently, ;B^Z, such as a hydrogen atom, a halogen atom, C1 - 6 alkyl groups, and a natural amino acid side chain, -- an aZ^ZR^{8Z} group (Z^Z -- a single bond.) -C(=O)-basis, a -C(=O) O-basis, a -CH₂O-basis, etc., R^{8Z} A hydrogen atom, C1 - 18 alkyl groups, C2 - 18 alkenyl groups, A b[, such as C2 - 18 alkynyl groups,]-CH₂NR^{9Z}R^{10Z} group or a -CONR^{9Z}R^{10Z} group (independently R^{9Z} and R^{10Z}, respectively) A hydrogen atom, C1 - 18 alkyl groups, C2 - 18 alkenyl groups, C2 - 18 alkynyl groups, etc., c) E^Z group (5, 6 member heterocycle which contain the hetero atom in which E^Z is chosen from a nitrogen atom, an oxygen atom, and a sulfur atom one or more), Or a d-CH₂E^Z group, a -C(=O) NHE^Z group, or a -C(=O) NHCH₂-E^Z group is expressed. It is indicated that the compound shown is useful as a PAF antagonist.

[0011]In the Patent Publication Heisei No. (WO-9314072) 502742 [seven to] specification, it is a general formula (W).

[Formula 7]



(Among a formula, W^W was arbitrarily replaced by one or more C1 - 6 alkyl-group substituents, and) Pyrid 3-yl groups, benzimidazole 1-yl groups, 4,5-imidazo[c] pyridine- 1-yl groups, 4,5-imidazo[c] pyridine- 3-yl groups and 4,5-imidazo[c] pyridine- 5-yl groups;Z^W The divalent alkanediyl group of aC2-12, An alkanediyl group, an alkynediyl group, etc. to b arbitration A hydroxyl group, -O (C1-6) alkyl group, the -(CH₂)_qU^W(CH₂)_r-basis (q -- 0 - 3;U^W -- benzenediyl.) replaced by one or more bases chosen from the halogen atom and the nitrile group -O-, -S-, a francdiyl

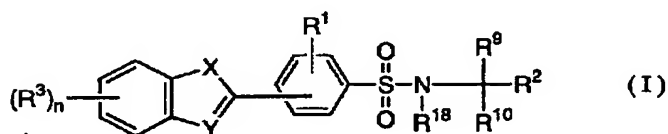
group, a thiophenediyl group, etc. -- etc. --; Q^W -- a carbonyl group. Thiocarbonyl group, sulfonyl group, or single bond; R^{1W} A hydrogen atom, R^{2W} , such as C1 - 6 alkyl groups, C2 - 6 alkenyl groups, etc. which were replaced by one or more bases arbitrarily chosen from C1 - 6 alkyl groups, -O (C1-6) alkyl group, the halogen atom, the $-CF_3$ group, and CN basis, a hydrogen atom, a halogen atom, C1 - 6 alkyl groups, C2 - 6 alkenyl groups which were arbitrarily replaced with one or more halogen atoms, $;$, such as a side chain of natural amino acid, -- R^{3W} -- hydrogen atom and halogen atom; B^W -- an $a-V^WR^{8W}$ group (V^W -- a $-C(=O)$ -basis.) R^{8W} , such as a $C(=O)O$ -basis and a $-CH_2O$ -basis, -A hydrogen atom, A b[, such as C1 - 18 alkyl groups, C2 - 6 alkenyl groups,]- $CH_2NR^{9W}R^{10W}$ group, a $-CONR^{9W}R^{10W}$ group, etc. are expressed. It is indicated that the compound shown is useful as a PAF antagonist. [0012]

[Objects of the Invention]Matrix [this invention persons] metalaw proteinase, for example, gelatinase, As a result of inquiring wholeheartedly in order to find out the compound which has inhibitory action to SUTOROMU lysin or collagenase, the new phenyl sulfonamide derivative shown by general formula (I) found out attaining the purpose.

[0013]

[Description of the Invention]This invention is 1 general-formula (I).

[Formula 8]



(R^1 among a formula a hydrogen atom, or C1 - 4 alkyl groups) [express and] R^2 expresses a $-COOR^4$ group or a $-CONHOR^5$ group, R^4 (1) hydrogen atom, (2) C1 - 8 alkyl group, and (3) phenyl group, Or (4) phenyl groups, a $-OCOR^6$ group (R^6 expresses C1 - 4 alkyl groups among a basis.), or a $-CONR^7R^8$ group (independently R^7 and R^8 among a basis, respectively) A hydrogen atom, or C1 - 4 alkyl groups is expressed. C1 replaced by either - 4 alkyl groups are expressed, [0014] R^5 expresses C1 replaced by the hydrogen atom, C1 - 8 alkyl groups, the phenyl group, or the phenyl group - 4 alkyl groups, X is an oxygen atom, a sulfur atom, or a $-NR^{17}$ group (R^{17} among a basis). A hydrogen atom, C1 - 4 alkyl groups, C1 replaced by the phenyl group - 4 alkyl groups, C1 replaced by C1 - 8 alkoxy carbonyl groups, or a phenyl group - 4 alkoxy carbonyl groups are expressed. It expresses, Y expresses CH basis or a nitrogen atom, and R^3 A hydrogen atom, C1 - 4 alkyl groups, C1 - 4 alkoxy groups, a halogen atom, a trifluoromethyl group, a hydroxyl group, A carboxyl group, C1 - 8 alkoxy carbonyl groups, a nitro group, a $-NR^7R^8$ group (among a basis) R^7 and R^8 express the same meaning as the above. Or a $-CONR^7R^8$ group (R^7 and R^8 express the same meaning as the above among a basis.) is expressed, and n expresses the integer of 1-4, [0015]Independently R^9 and R^{10} , respectively (1) hydrogen atom, (2) C1 - 8 alkyl groups (however, one $-CH_2$ -basis in an alkyl group may be changed with one sulfur atom.), a (3)- COR^{11} group (the inside of a basis, and R^{11} -- a hydroxyl group and C -- one to 8 alkyl group) C1 - 4 alkoxy groups, or the $-NR^{15}R^{16}$ group (independently R^{15} and R^{16} among a basis, respectively) replaced by C1 - 8 alkoxy groups, the phenoxy group, and the phenyl group C1 replaced by the hydrogen atom, C1 - 4 alkyl groups, the phenyl group, one piece, or two phenyl groups - 4 alkyl groups are expressed. It expresses. (4) a ring group and (5) heterocycle groups (the

ring of the above (4) or the heterocycle of the above (5) may be replaced by one to three C1 - 4 alkyl groups, C1 - 4 alkoxy groups, the halogen atom, the hydroxyl group, and the trifluoromethyl group.) -- or [0016](6) C1 replaced by one basis chosen from the following (i) - (viii) - 8 alkyl groups, (i) A -COR¹¹ group (R¹¹ expresses the same meaning as the above among a basis.), (ii) C1 - 4 alkoxy groups, a (iii) hydroxyl group, a (iv) benzyloxy group, (v) A guanidino group, a (vi) -NR¹²R¹³ group (independently R¹² and R¹³ among a basis, respectively) A hydrogen atom, C1 - 4 alkyl groups, or a COOR¹⁴ group (among a basis) R¹⁴ expresses C1 - 4 alkyl groups, or benzyl. It expresses. (vii) Express a ring group or a (viii) heterocycle group (the ring of said (vii) or the heterocycle of said (viii) may be replaced by one to three C1 - 4 alkyl groups, C1 - 4 alkoxy groups, the halogen atom, the hydroxyl group, and the trifluoromethyl group.), [0017]C1 by which R¹⁸ was replaced by the hydrogen atom, C1 - 4 alkyl groups, and the phenyl group - 4 alkyl groups, C1 replaced by C1 - 8 alkoxy carbonyl groups, or a phenyl group - 4 alkoxy carbonyl groups are expressed. The phenyl sulfonamide derivatives shown or those nontoxic salts, [0018]2) It is related with the drugs which contain the manufacturing method of the phenyl sulfonamide derivatives shown by general formula (I), and those nontoxic salts, the phenyl sulfonamide derivatives shown by 3 general-formula (I), and those nontoxic salts as an active principle.

[0019]Especially in this invention, it points, and as long as there is nothing, an isomer includes this all. For example, the thing of a straight chain and the thing of a branched chain are contained in an alkyl group, an alkoxy group, and an alkylene group. The double bond in an alkenylene group contains what is E, Z, and EZ mixture. The isomer produced by existence of asymmetric carbon atoms in case the alkyl group, ARUKOSHIKI group, and alkylene group of a branched chain exist is also contained. [0020]The inside of general formula (I), R¹, R³, R⁶, R⁷, R⁸, R¹², R¹³, R¹⁴, C1 - 4 alkyl groups, or R⁴ expressed by R¹⁵, R¹⁶, R¹⁷, and R¹⁸, C1 - 4 alkyl groups (the substituent of a ring group or a heterocycle group is also included.) in R⁵, R⁹, R¹⁰, R¹⁵, R¹⁶, R¹⁷, and R¹⁸ are methyl, ethyl, propyl, butyl groups, and these isomers. The inside of general formula (I), R⁴, R⁵, R⁶, R¹⁰, C1 - 8 alkyl groups in C1 expressed by R¹¹ - 8 alkyl groups or R⁹, and R¹⁰ are methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl groups, and these isomers. One -CH₂-basis expressed by R⁹ and R¹⁰ among general formula (I) with C1 replaced with one sulfur atom - 8 alkyl groups. Methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, an octyl group, and one -CH₂-basis in these isomer groups express the basis changed with one sulfur atom. For example, a -SH, -CH₂-SH, and -CH₂CH₂-S-CH₃ group is mentioned.

[0021]C1 - 4 alkoxy groups, or R⁹ expressed by R³ among general formula (I), C1 - 4 alkoxy groups (the substituent of a ring group or a heterocycle group is also included.) in R¹⁰ and R¹¹ are methoxy and ethoxy ** propoxy, butoxy groups, and these isomers. C1 expressed by R¹¹ - 8 alkoxy groups are methoxy and ethoxy ** propoxy, butoxy, pentyloxy one, hexyloxy one, heptyloxy, octyloxy groups, and these isomers among general formula (I).

[0022]With C1 expressed by R³, R¹⁷, and R¹⁸ among general formula (I) - 8 alkoxy carbonyl groups. They are carbomethoxy, ethoxycarbonyl, carbopropoxy, butoxycarbonyl, pentyloxy carbonyl, hexyloxy carbonyl, heptyloxy carbonyl, octyloxy carbonyl groups, and these isomers. C1 - 4 alkoxy carbonyl groups in R¹⁷ and R¹⁸ are carbomethoxy, ethoxycarbonyl, carbopropoxy, butoxycarbonyl groups, and these isomers among general formula (I).

[0023]The ring in R⁹ and R¹⁰ means the with a carbon number of 15 or less of a monocycle and two rings aromatic ring in which all may be saturated in part among

general formula (I). As these rings, the ring with which benzene, naphthalene, indene, an azulene, a fluorene, the phenanthrene, anthracene, an acenaphthylene, biphenylene rings and these parts, or all are saturated is mentioned, for example. The monocycle of 5 - 15 member or 2 cyclic heterocycle containing one piece or two nitrogen atoms, one oxygen atom, and/or one sulfur atom is expressed as the heterocycle in R^9 and R^{10} among general formula (I). With the monocycle of 5 - 15 member or 2 cyclic heterocycle containing one piece or two nitrogen atoms, one oxygen atom, and/or one sulfur atom. The monocycle of 5 containing one piece or two nitrogen atoms, one oxygen atom, and/or one sulfur atom - 15 members, 2 cyclic heterocyclic aryl, or its in part or all saturated thing is contained.

[0024]As the monocycle of 5 containing above mentioned one piece or two nitrogen atoms, one oxygen atom, and/or one sulfur atom - 15 members, or 2 cyclic heterocyclic aryl, Pyrrole, imidazole, a pyrazole, pyridine, pyrazine, pyrimidine, Pyridazine, azepine, diazepine, a furan, Piran, oxepin, Oxazepine, a thiophene, thiazine (thiopyran), thiepine, oxazol, An isoxazole, a thiazole, isothiazole, oxadiazole, An oxazine, oxa diazine, oxa azepine, oxa diazepine, Thiadiazole, a thiazine, thiadiazin, thia azepine, thia diazepine, Indole, isoindole, benzofuran, isobenzofuran, benzothiophene, Isobenzothiophene, indazole, quinoline, an isoquinoline, phthalazine, NAFUCHI lysine, quinoxaline, quinazoline, cinnoline, benzooxazol, benzothiazole, a benzimidazole ring, etc. are mentioned.

[0025]As what was in part or all saturated with the monocycle of 5 - 15 member or 2 cyclic heterocycle containing above mentioned one piece or two nitrogen atoms, one oxygen atom, and/or one sulfur atom, Pyrrolidine, pyrrolidine, imidazoline, imidazolidine, pyrazoline, Pyrazolidine, piperidine, a piperazine, tetrahydro pyrimidine, Tetrahydro pyridazine, dihydrofuran, a tetrahydrofuran, a dihydropyran, Tetrahydropyran, a dihydrothiophene, tetrahydrothiophene, Dihydrothiazine (dihydrothiopyran), tetrahydro thiazine (tetrahydro thiopyran), Dihydrooxazol, tetrahydro oxazol, a dihydroisoxazole, A tetrahydro isoxazole, a dihydrothiazole, a tetrahydro thiazole, Dihydroisothiazole, tetrahydro isothiazole, morpholine, Thiomorpholine, indoline, isoindoline, dihydrobenzofuran, Par hydronaliumbenzofuran, dihydroisobenzofuran, par hydronaliumisobenzofuran, dihydrobenzothiophene, par hydronalium benzothiophene, dihydroiso benzothiophene, par hydronaliumiso benzothiophene, Dihydroindazole, par hydronalium indazole, dihydroquinoline, Tetrahydroquinoline, par hydronaliumquinoline, a dihydroisoquinoline, Tetrahydroisoquinoline, a par hydronaliumisoquinoline, dihydrophthalazine, Tetrahydro phthalazine, par hydronaliumphthalazine, dihydroNAFUCHI lysine, Tetrahydro NAFUCHI lysine, par hydronalium NAFUCHI lysine, dihydroquinoxaline, Tetrahydro quinoxaline, par hydronaliumquinoxaline, dihydroquinazoline, Tetrahydro quinazoline, par hydronaliumquinazoline, dihydrocinnoline, Tetrahydro cinnoline, par hydronalium cinnoline, dihydrobenzooxazol, par hydronaliumbenzooxazol, dihydrobenzothiazole, par hydronaliumbenzothiazole, dihydrobenzimidazole, a par hydronaliumbenzimidazole ring, etc. are mentioned.

[0026]The halogen atom as the ring group in the halogen atom or R^9 expressed by R^3 , and R^{10} or a substituent of a heterocycle group means chlorine, bromine, fluoride, and iodine atoms among general formula (I). R^9 and R^{10} may express an alpha-amino-acid side chain among general formula (I). As alpha-amino acid, a glycine, an alanine, serine, threonine, Cystein, valine, methionine, leucine, isoleucine, phenylalanine, tyrosine, aspartic acid, glutamic acid, asparagine, arginine, lysine, histidine, tryptophan, glutamine, etc. are mentioned. An alpha-amino-acid derivative is

contained in the alpha-amino acid, and the alpha-amino acid of D object, L object and DL mixtures, or those ARO objects is also contained in it.

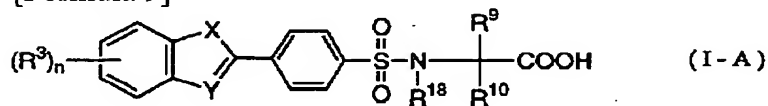
[0027]

[Salt] All the nontoxic salts are included in this invention. For example, a general salt, acid addition salt, a hydrate salt, etc. are mentioned. this invention compound shown by general formula (I) is changed into a salt corresponding by a publicly known method. The water-soluble thing of a salt without toxicity is preferred. As a suitable salt, the salt of alkaline metals (potassium, sodium, etc.), The salt of alkaline-earth metals (calcium, magnesium, etc.), ammonium salt, the organic amine (tetramethylammonium and triethylamine.) permitted pharmacologically Salts, such as methylamine, dimethylamine, cyclopentyl amine, benzylamine, phenethylamine, piperidine, monoethanolamine, diethanolamine, tris(hydroxymethyl) amine, lysine, arginine, and an N-methyl-D-glucamine, are mentioned.

[0028]this invention compound shown by general formula (I) is changed into acid addition salt corresponding by a publicly known method. The water-soluble thing of acid addition salt without toxicity is preferred. As suitable acid addition salt, a hydrochloride, the hydrobromate, sulfate, an phosphate, An inorganic acid salt like a nitrate or acetate, trifluoroacetate, a lactate, A tartrate, an oxalate, fumaric acid chloride, a maleate, citrate, a benzoate, methanesulfon acid chloride, an ethanesulfonic-acid salt, a benzenesulfonic acid salt, a toluenesulfonic acid salt, an isethionic acid salt, a glucuronic acid salt, and organic acid salt like gluconate are mentioned. this invention compound shown by general formula (I) or its salt is also convertible for a hydrate by a publicly known method.

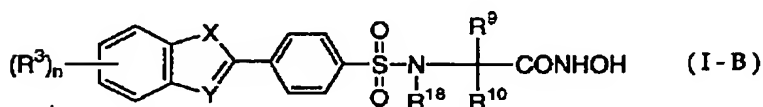
[0029]As a desirable compound among this invention compounds shown by general formula (I), it is a general formula (I-A).

[Formula 9]



(all the signs express the same meaning as the above among a formula.) -- the compound shown and general formula (I-B)

[Formula 10]

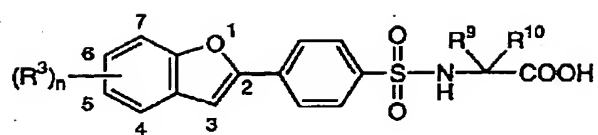


(all the signs express the same meaning as the above among a formula.) -- the compound shown is mentioned. The compound indicated from the following table 1 to Table 32, the compound indicated in those nontoxic salts and examples, etc. are mentioned more preferably. Me expresses a methyl group among front [following each].

[0030]

[Table 1]

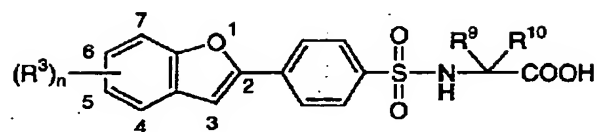
表 1



番号	$(R^3)_n$ —	R^9 R^{10}	番号	$(R^3)_n$ —	R^9 R^{10}
1	H		6	5-CH ₃	
2	H		7	5-CH ₃	
3	H		8	5-CH ₃	
4	H		9	5-CH ₃	
5	H		10	5-CH ₃	

[0031]
[Table 2]

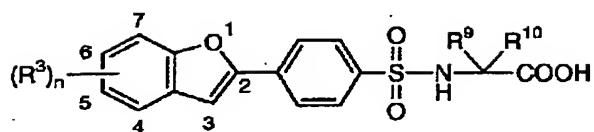
表 1 (つづき)



番号	(R ³) _n —	$\begin{array}{c} R^9 \\ \diagup \quad \diagdown \\ R^{10} \end{array}$	番号	(R ³) _n —	$\begin{array}{c} R^9 \\ \diagup \quad \diagdown \\ R^{10} \end{array}$
1 1	6-CH ₃		1 6	5,6-diCH ₃	
1 2	6-CH ₃		1 7	5,6-diCH ₃	
1 3	6-CH ₃		1 8	5,6-diCH ₃	
1 4	6-CH ₃		1 9	5,6-diCH ₃	
1 5	6-CH ₃		2 0	5,6-diCH ₃	

[0032]
[Table 3]

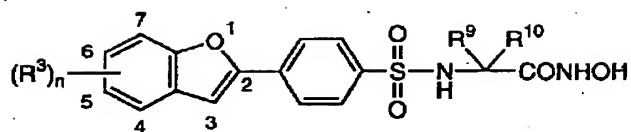
表1 (つづき)



番号	(R ³) _n —	$\begin{array}{c} R^9 \\ \diagup \\ R^{10} \end{array}$	番号	(R ³) _n —	$\begin{array}{c} R^9 \\ \diagup \\ R^{10} \end{array}$
2 1	5-OCH ₃		2 6	6-OCH ₃	
2 2	5-OCH ₃		2 7	6-OCH ₃	
2 3	5-OCH ₃		2 8	6-OCH ₃	
2 4	5-OCH ₃		2 9	6-OCH ₃	
2 5	5-OCH ₃		3 0	6-OCH ₃	

[0033]
[Table 4]

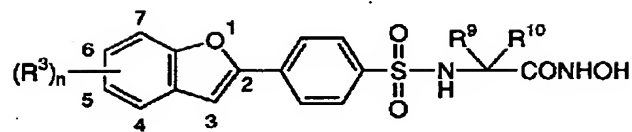
表 2



番号	$(R^3)_n$ —	R^9 R^{10}	番号	$(R^3)_n$ —	R^9 R^{10}
1	H		6	5-CH ₃	
2	H		7	5-CH ₃	
3	H		8	5-CH ₃	
4	H		9	5-CH ₃	
5	H		10	5-CH ₃	

[0034]
[Table 5]

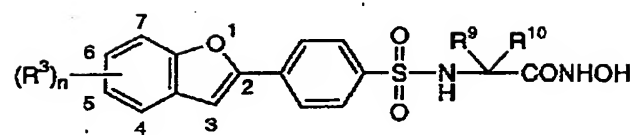
表2 (つづき)



番号	(R ³) _n —	$\begin{array}{c} R^9 \\ \diagup \quad \diagdown \\ R^{10} \end{array}$	番号	(R ³) _n —	$\begin{array}{c} R^9 \\ \diagup \quad \diagdown \\ R^{10} \end{array}$
1 1	6-CH ₃		1 6	5,6-diCH ₃	
1 2	6-CH ₃		1 7	5,6-diCH ₃	
1 3	6-CH ₃		1 8	5,6-diCH ₃	
1 4	6-CH ₃		1 9	5,6-diCH ₃	
1 5	6-CH ₃		2 0	5,6-diCH ₃	

[0035]
[Table 6]

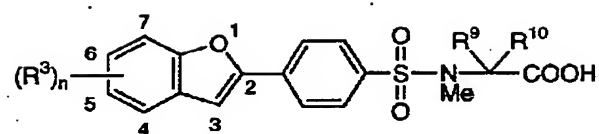
表2 (つづき)



番号	(R³) _n —	$\begin{array}{c} \text{R}^9 \quad \text{R}^{10} \\ \diagdown \quad \diagup \\ \text{C} \end{array}$	番号	(R³) _n —	$\begin{array}{c} \text{R}^9 \quad \text{R}^{10} \\ \diagdown \quad \diagup \\ \text{C} \end{array}$
2 1	5-OCH ₃		2 6	6-OCH ₃	
2 2	5-OCH ₃		2 7	6-OCH ₃	
2 3	5-OCH ₃		2 8	6-OCH ₃	
2 4	5-OCH ₃		2 9	6-OCH ₃	
2 5	5-OCH ₃		3 0	6-OCH ₃	

[0036]
[Table 7]

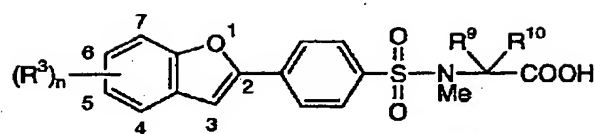
表 3



番号	$(R^3)_n$ —	R^9 R^{10}	番号	$(R^3)_n$ —	R^9 R^{10}
1	H		6	5-CH ₃	
2	H		7	5-CH ₃	
3	H		8	5-CH ₃	
4	H		9	5-CH ₃	
5	H		10	5-CH ₃	

[0037]
[Table 8]

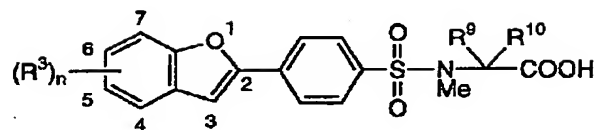
表3 (つづき)



番号	(R ³) _n —	$\begin{array}{c} \text{R}^9 \quad \text{R}^{10} \\ \diagdown \quad \diagup \\ \text{C} \end{array}$	番号	(R ³) _n —	$\begin{array}{c} \text{R}^9 \quad \text{R}^{10} \\ \diagdown \quad \diagup \\ \text{C} \end{array}$
1 1	6-CH ₃		1 6	5,6-diCH ₃	
1 2	6-CH ₃		1 7	5,6-diCH ₃	
1 3	6-CH ₃		1 8	5,6-diCH ₃	
1 4	6-CH ₃		1 9	5,6-diCH ₃	
1 5	6-CH ₃		2 0	5,6-diCH ₃	

[0038]
[Table 9]

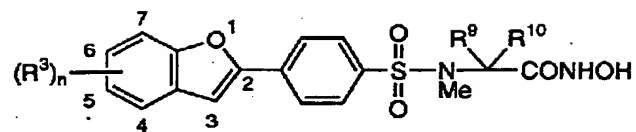
表3 (つづき)



番号	(R ³) _n —	R ⁹ R ¹⁰	番号	(R ³) _n —	R ⁹ R ¹⁰
2 1	5-OCH ₃		2 6	6-OCH ₃	
2 2	5-OCH ₃		2 7	6-OCH ₃	
2 3	5-OCH ₃		2 8	6-OCH ₃	
2 4	5-OCH ₃		2 9	6-OCH ₃	
2 5	5-OCH ₃		3 0	6-OCH ₃	

[0039]
[Table 10]

表 4

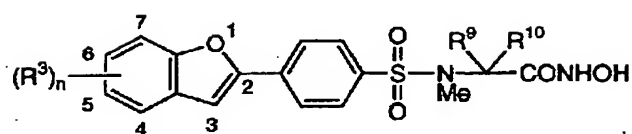


番号	(R ³) _n —	$\begin{array}{c} \text{R}^9 \quad \text{R}^{10} \\ \diagdown \quad \diagup \\ \text{C} \end{array}$	番号	(R ³) _n —	$\begin{array}{c} \text{R}^9 \quad \text{R}^{10} \\ \diagdown \quad \diagup \\ \text{C} \end{array}$
1	H		6	5-CH ₃	
2	H		7	5-CH ₃	
3	H		8	5-CH ₃	
4	H		9	5-CH ₃	
5	H		10	5-CH ₃	

[0040]

[Table 11]

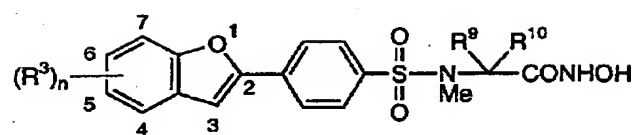
表4 (つづき)



番号	(R ³) _n —	$\begin{array}{c} R^9 \\ \diagup \quad \diagdown \\ R^{10} \end{array}$	番号	(R ³) _n —	$\begin{array}{c} R^9 \\ \diagup \quad \diagdown \\ R^{10} \end{array}$
1 1	6-CH ₃		1 6	5,6-diCH ₃	
1 2	6-CH ₃		1 7	5,6-diCH ₃	
1 3	6-CH ₃		1 8	5,6-diCH ₃	
1 4	6-CH ₃		1 9	5,6-diCH ₃	
1 5	6-CH ₃		2 0	5,6-diCH ₃	

[0041]
[Table 12]

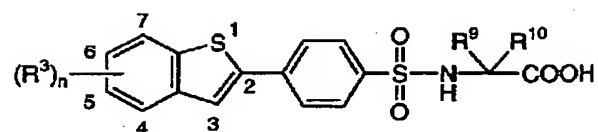
表 4 (つづき)



番号	(R³) _n —	$\begin{array}{c} \text{R}^9 \quad \text{R}^{10} \\ \diagdown \quad \diagup \\ \text{C} \end{array}$	番号	(R³) _n —	$\begin{array}{c} \text{R}^9 \quad \text{R}^{10} \\ \diagdown \quad \diagup \\ \text{C} \end{array}$
2 1	5-OCH ₃		2 6	6-OCH ₃	
2 2	5-OCH ₃		2 7	6-OCH ₃	
2 3	5-OCH ₃		2 8	6-OCH ₃	
2 4	5-OCH ₃		2 9	6-OCH ₃	
2 5	5-OCH ₃		3 0	6-OCH ₃	

[0042]
[Table 13]

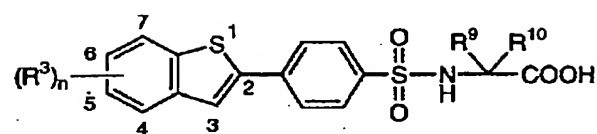
表 5



番号	(R ³) _n —	$\begin{array}{c} R^9 \\ \diagup \quad \diagdown \\ R^{10} \end{array}$	番号	(R ³) _n —	$\begin{array}{c} R^9 \\ \diagup \quad \diagdown \\ R^{10} \end{array}$
1	H		6	5-CH ₃	
2	H		7	5-CH ₃	
3	H		8	5-CH ₃	
4	H		9	5-CH ₃	
5	H		10	5-CH ₃	

[0043]
[Table 14]

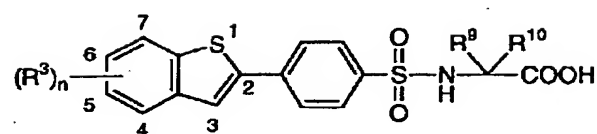
表5 (つづき)



番号	(R ³) _n —	R ⁹ R ¹⁰	番号	(R ³) _n —	R ⁹ R ¹⁰
1 1	6-CH ₃		1 6	5,6-diCH ₃	
1 2	6-CH ₃		1 7	5,6-diCH ₃	
1 3	6-CH ₃		1 8	5,6-diCH ₃	
1 4	6-CH ₃		1 9	5,6-diCH ₃	
1 5	6-CH ₃		2 0	5,6-diCH ₃	

[0044]
[Table 15]

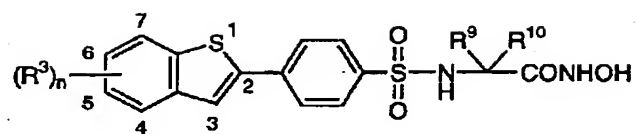
表 5 (つづき)



番号	(R ³) _n —	$\begin{array}{c} R^9 \\ \diagup \quad \diagdown \\ R^{10} \end{array}$	番号	(R ³) _n —	$\begin{array}{c} R^9 \\ \diagup \quad \diagdown \\ R^{10} \end{array}$
2 1	5-OCH ₃		2 6	6-OCH ₃	
2 2	5-OCH ₃		2 7	6-OCH ₃	
2 3	5-OCH ₃		2 8	6-OCH ₃	
2 4	5-OCH ₃		2 9	6-OCH ₃	
2 5	5-OCH ₃		3 0	6-OCH ₃	

[0045]
[Table 16]

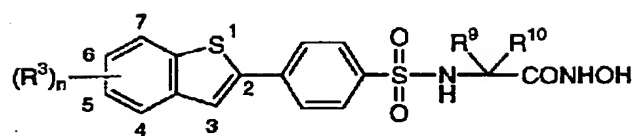
表 6



番号	(R ³) _n —	R ⁹ R ¹⁰	番号	(R ³) _n —	R ⁹ R ¹⁰
1	H		6	5-CH ₃	
2	H		7	5-CH ₃	
3	H		8	5-CH ₃	
4	H		9	5-CH ₃	
5	H		10	5-CH ₃	

[0046]
[Table 17]

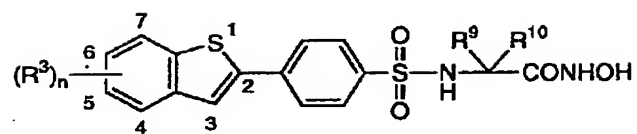
表6 (つづき)



番号	(R ³) _n —	R ⁹ R ¹⁰	番号	(R ³) _n —	R ⁹ R ¹⁰
1 1	6-CH ₃		1 6	5,6-diCH ₃	
1 2	6-CH ₃		1 7	5,6-diCH ₃	
1 3	6-CH ₃		1 8	5,6-diCH ₃	
1 4	6-CH ₃		1 9	5,6-diCH ₃	
1 5	6-CH ₃		2 0	5,6-diCH ₃	

[0047]
[Table 18]

表 6 (つづき)

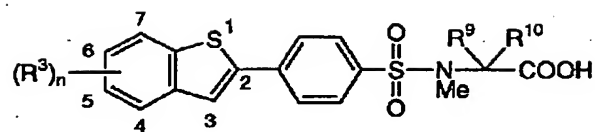


番号	(R ³) _n —	$\begin{matrix} R^9 & R^{10} \\ \diagdown & / \end{matrix}$	番号	(R ³) _n —	$\begin{matrix} R^9 & R^{10} \\ \diagdown & / \end{matrix}$
2 1	5-OCH ₃		2 6	6-OCH ₃	
2 2	5-OCH ₃		2 7	6-OCH ₃	
2 3	5-OCH ₃		2 8	6-OCH ₃	
2 4	5-OCH ₃		2 9	6-OCH ₃	
2 5	5-OCH ₃		3 0	6-OCH ₃	

[0048]

[Table 19]

表 7

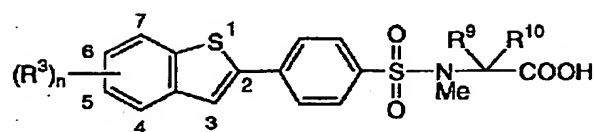


番号	(R ³) _n —	R ⁹ R ¹⁰	番号	(R ³) _n —	R ⁹ R ¹⁰
1	H		6	5-CH ₃	
2	H		7	5-CH ₃	
3	H		8	5-CH ₃	
4	H		9	5-CH ₃	
5	H		10	5-CH ₃	

[0049]

[Table 20]

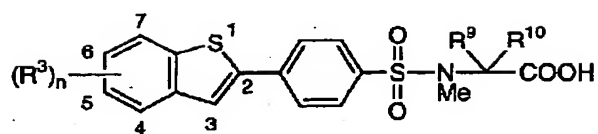
表7 (つづき)



番号	(R ³) _n —	$\begin{array}{c} \text{R}^9 \\ \diagup \quad \diagdown \\ \text{C} \end{array}$ $\begin{array}{c} \text{R}^{10} \end{array}$	番号	(R ³) _n —	$\begin{array}{c} \text{R}^9 \\ \diagup \quad \diagdown \\ \text{C} \end{array}$ $\begin{array}{c} \text{R}^{10} \end{array}$
1 1	6-CH ₃		1 6	5,6-diCH ₃	
1 2	6-CH ₃		1 7	5,6-diCH ₃	
1 3	6-CH ₃		1 8	5,6-diCH ₃	
1 4	6-CH ₃		1 9	5,6-diCH ₃	
1 5	6-CH ₃		2 0	5,6-diCH ₃	

[0050]
[Table 21]

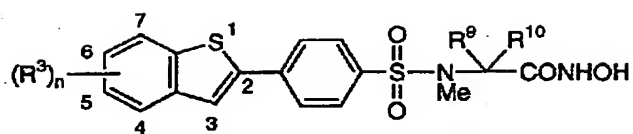
表7 (つづき)



番号	(R ³) _n —	$\begin{array}{c} R^9 \\ \diagup \quad \diagdown \\ R^{10} \end{array}$	番号	(R ³) _n —	$\begin{array}{c} R^9 \\ \diagup \quad \diagdown \\ R^{10} \end{array}$
2 1	5-OCH ₃		2 6	6-OCH ₃	
2 2	5-OCH ₃		2 7	6-OCH ₃	
2 3	5-OCH ₃		2 8	6-OCH ₃	
2 4	5-OCH ₃		2 9	6-OCH ₃	
2 5	5-OCH ₃		3 0	6-OCH ₃	

[0051]
[Table 22]

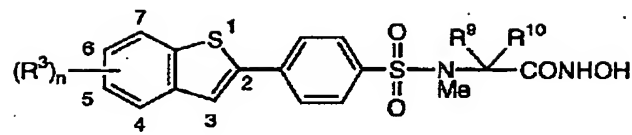
表 8



番号	(R ³) _n —	R ⁹ R ¹⁰	番号	(R ³) _n —	R ⁹ R ¹⁰
1	H		6	5-CH ₃	
2	H		7	5-CH ₃	
3	H		8	5-CH ₃	
4	H		9	5-CH ₃	
5	H		10	5-CH ₃	

[0052]
[Table 23]

表 8 (つづき)

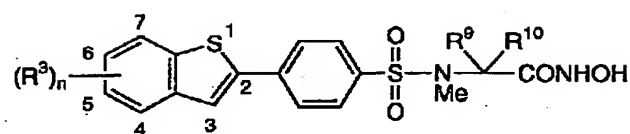


番号	(R ³) _n —	$\begin{array}{c} R^9 \\ \diagup \quad \diagdown \\ R^{10} \end{array}$	番号	(R ³) _n —	$\begin{array}{c} R^9 \\ \diagup \quad \diagdown \\ R^{10} \end{array}$
1 1	6-CH ₃		1 6	5,6-diCH ₃	
1 2	6-CH ₃		1 7	5,6-diCH ₃	
1 3	6-CH ₃		1 8	5,6-diCH ₃	
1 4	6-CH ₃		1 9	5,6-diCH ₃	
1 5	6-CH ₃		2 0	5,6-diCH ₃	

[0053]

[Table 24]

表8 (つづき)

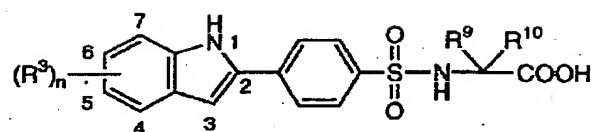


番号	(R ³) _n —	R ⁹ R ¹⁰	番号	(R ³) _n —	R ⁹ R ¹⁰
2 1	5-OCH ₃		2 6	6-OCH ₃	
2 2	5-OCH ₃		2 7	6-OCH ₃	
2 3	5-OCH ₃		2 8	6-OCH ₃	
2 4	5-OCH ₃		2 9	6-OCH ₃	
2 5	5-OCH ₃		3 0	6-OCH ₃	

[0054]

[Table 25]

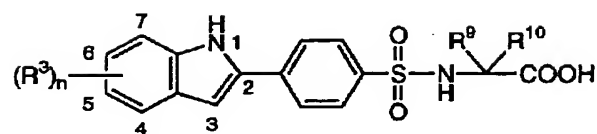
表 9



番号	(R³) _n —	$\begin{array}{c} R^9 \\ \diagup \quad \diagdown \\ R^{10} \end{array}$	番号	(R³) _n —	$\begin{array}{c} R^9 \\ \diagup \quad \diagdown \\ R^{10} \end{array}$
1	H		6	5-CH ₃	
2	H		7	5-CH ₃	
3	H		8	5-CH ₃	
4	H		9	5-CH ₃	
5	H		10	5-CH ₃	

[0055]
[Table 26]

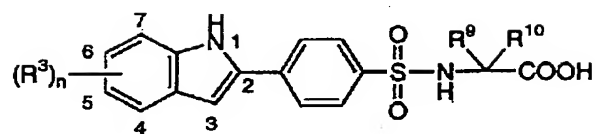
表9 (つづき)



番号	(R ³) _n —	R ⁹ R ¹⁰	番号	(R ³) _n —	R ⁹ R ¹⁰
1 1	6-CH ₃		1 6	5,6-diCH ₃	
1 2	6-CH ₃		1 7	5,6-diCH ₃	
1 3	6-CH ₃		1 8	5,6-diCH ₃	
1 4	6-CH ₃		1 9	5,6-diCH ₃	
1 5	6-CH ₃		2 0	5,6-diCH ₃	

[0056]
[Table 27]

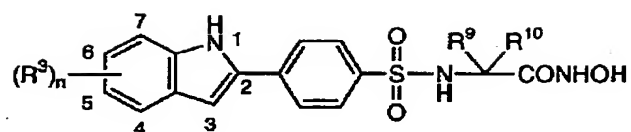
表9 (つづき)



番号	(R ³) _n —	R ⁹ R ¹⁰	番号	(R ³) _n —	R ⁹ R ¹⁰
2 1	5-OCH ₃		2 6	6-OCH ₃	
2 2	5-OCH ₃		2 7	6-OCH ₃	
2 3	5-OCH ₃		2 8	6-OCH ₃	
2 4	5-OCH ₃		2 9	6-OCH ₃	
2 5	5-OCH ₃		3 0	6-OCH ₃	

[0057]
[Table 28]

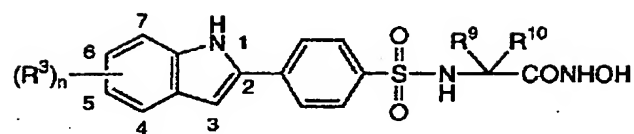
表 10



番号	(R ³) _n —	R ⁹ R ¹⁰	番号	(R ³) _n —	R ⁹ R ¹⁰
1	H		6	5-CH ₃	
2	H		7	5-CH ₃	
3	H		8	5-CH ₃	
4	H		9	5-CH ₃	
5	H		10	5-CH ₃	

[0058]
[Table 29]

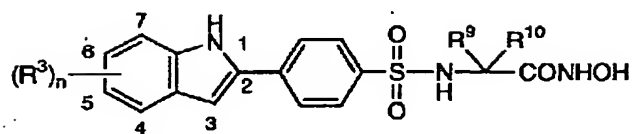
表 10 (つづき)



番号	(R ³) _n —	R ⁹ R ¹⁰	番号	(R ³) _n —	R ⁹ R ¹⁰
1 1	6-CH ₃		1 6	5,6-diCH ₃	
1 2	6-CH ₃		1 7	5,6-diCH ₃	
1 3	6-CH ₃		1 8	5,6-diCH ₃	
1 4	6-CH ₃		1 9	5,6-diCH ₃	
1 5	6-CH ₃		2 0	5,6-diCH ₃	

[0059]
[Table 30]

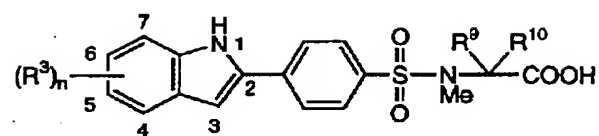
表10 (つづき)



番号	(R ⁹) _n —	R ⁹ R ¹⁰	番号	(R ³) _n —	R ⁹ R ¹⁰
2 1	5-OCH ₃		2 6	6-OCH ₃	
2 2	5-OCH ₃		2 7	6-OCH ₃	
2 3	5-OCH ₃		2 8	6-OCH ₃	
2 4	5-OCH ₃		2 9	6-OCH ₃	
2 5	5-OCH ₃		3 0	6-OCH ₃	

[0060]
[Table 31]

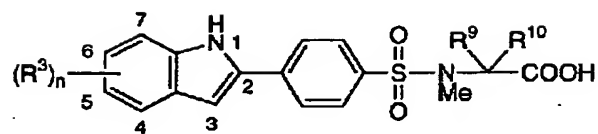
表 11



番号	(R³) _n —	R⁹ R¹⁰	番号	(R³) _n —	R⁹ R¹⁰
1	H		6	5-CH₃	
2	H		7	5-CH₃	
3	H		8	5-CH₃	
4	H		9	5-CH₃	
5	H		10	5-CH₃	

[0061]
[Table 32]

表 1 1 (つづき)

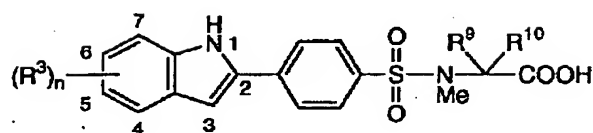


番号	(R ³) _n —	R ⁹ R ¹⁰	番号	(R ³) _n —	R ⁹ R ¹⁰
1 1	6-CH ₃		1 6	5,6-diCH ₃	
1 2	6-CH ₃		1 7	5,6-diCH ₃	
1 3	6-CH ₃		1 8	5,6-diCH ₃	
1 4	6-CH ₃		1 9	5,6-diCH ₃	
1 5	6-CH ₃		2 0	5,6-diCH ₃	

[0062]

[Table 33]

表 1 1 (つづき)

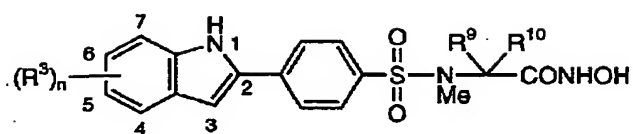


番号	(R ³) _n —	R ⁹ R ¹⁰	番号	(R ³) _n —	R ⁹ R ¹⁰
2 1	5-OCH ₃		2 6	6-OCH ₃	
2 2	5-OCH ₃		2 7	6-OCH ₃	
2 3	5-OCH ₃		2 8	6-OCH ₃	
2 4	5-OCH ₃		2 9	6-OCH ₃	
2 5	5-OCH ₃		3 0	6-OCH ₃	

[0063]

[Table 34]

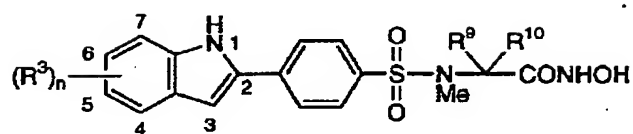
表 1 2



番号	(R³) _n —	$\begin{matrix} R^9 & R^{10} \\ \diagdown & / \end{matrix}$	番号	(R³) _n —	$\begin{matrix} R^9 & R^{10} \\ \diagdown & / \end{matrix}$
1	H		6	5-CH ₃	
2	H		7	5-CH ₃	
3	H		8	5-CH ₃	
4	H		9	5-CH ₃	
5	H		10	5-CH ₃	

[0064]
[Table 35]

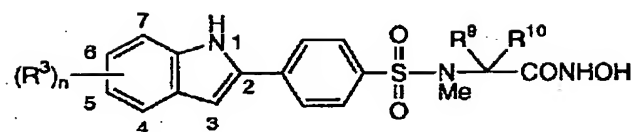
表12 (つづき)



番号	(R³) _n —	$\begin{array}{c} R^9 \\ \diagup \quad \diagdown \\ R^9 \quad R^{10} \end{array}$	番号	(R³) _n —	$\begin{array}{c} R^9 \\ \diagup \quad \diagdown \\ R^9 \quad R^{10} \end{array}$
11	6-CH ₃		16	5,6-diCH ₃	
12	6-CH ₃		17	5,6-diCH ₃	
13	6-CH ₃		18	5,6-diCH ₃	
14	6-CH ₃		19	5,6-diCH ₃	
15	6-CH ₃		20	5,6-diCH ₃	

[0065]
[Table 36]

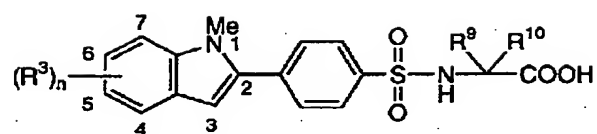
表 12 (つづき)



番号	(R ³) _n —	R ⁹ R ¹⁰	番号	(R ³) _n —	R ⁹ R ¹⁰
2 1	5-OCH ₃		2 6	6-OCH ₃	
2 2	5-OCH ₃		2 7	6-OCH ₃	
2 3	5-OCH ₃		2 8	6-OCH ₃	
2 4	5-OCH ₃		2 9	6-OCH ₃	
2 5	5-OCH ₃		3 0	6-OCH ₃	

[0066]
[Table 37]

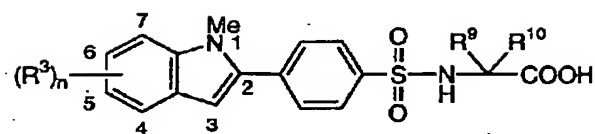
表 13



番号	(R ³) _n —	R ⁹ R ¹⁰	番号	(R ³) _n —	R ⁹ R ¹⁰
1	H		6	5-CH ₃	
2	H		7	5-CH ₃	
3	H		8	5-CH ₃	
4	H		9	5-CH ₃	
5	H		10	5-CH ₃	

[0067]
[Table 38]

表 13 (つづき)

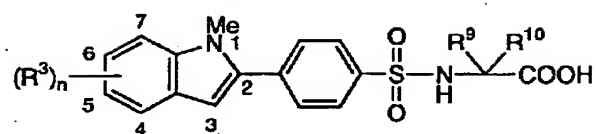


番号	(R ³) _n —	R ⁹ R ¹⁰	番号	(R ³) _n —	R ⁹ R ¹⁰
1 1	6-CH ₃		1 6	5,6-diCH ₃	
1 2	6-CH ₃		1 7	5,6-diCH ₃	
1 3	6-CH ₃		1 8	5,6-diCH ₃	
1 4	6-CH ₃		1 9	5,6-diCH ₃	
1 5	6-CH ₃		2 0	5,6-diCH ₃	

[0068]

[Table 39]

表 13. (つづき)

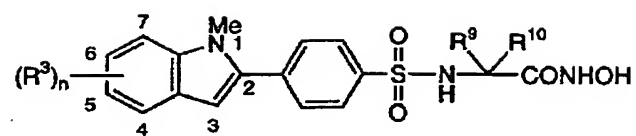


番号	(R ³) _n —	R ⁹ R ¹⁰	番号	(R ³) _n —	R ⁹ R ¹⁰
2 1	5-OCH ₃		2 6	6-OCH ₃	
2 2	5-OCH ₃		2 7	6-OCH ₃	
2 3	5-OCH ₃		2 8	6-OCH ₃	
2 4	5-OCH ₃		2 9	6-OCH ₃	
2 5	5-OCH ₃		3 0	6-OCH ₃	

[0069]

[Table 40]

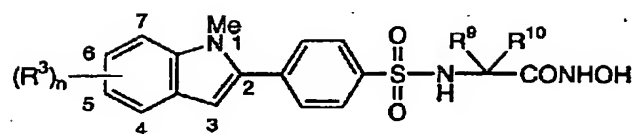
表 1 4



番号	(R ³) _n —	$\begin{matrix} R^9 & R^{10} \\ \diagdown & / \end{matrix}$	番号	(R ³) _n —	$\begin{matrix} R^9 & R^{10} \\ \diagdown & / \end{matrix}$
1	H		6	5-CH ₃	
2	H		7	5-CH ₃	
3	H		8	5-CH ₃	
4	H		9	5-CH ₃	
5	H		10	5-CH ₃	

[0070]
[Table 41]

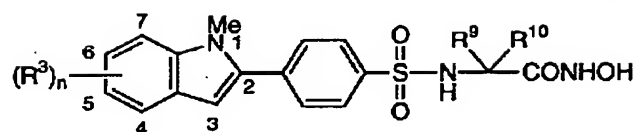
表 14 (つづき)



番号	(R ³) _n —	R ⁹ R ¹⁰	番号	(R ³) _n —	R ⁹ R ¹⁰
1 1	6-CH ₃		1 6	5,6-diCH ₃	
1 2	6-CH ₃		1 7	5,6-diCH ₃	
1 3	6-CH ₃		1 8	5,6-diCH ₃	
1 4	6-CH ₃		1 9	5,6-diCH ₃	
1 5	6-CH ₃		2 0	5,6-diCH ₃	

[0071]
[Table 42]

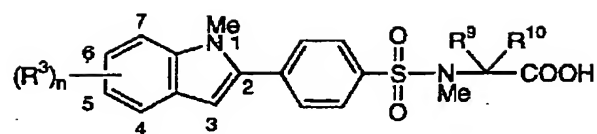
表 1 4 (つづき)



番号	(R³) _n —	R⁹ R¹⁰	番号	(R³) _n —	R⁹ R¹⁰
2 1	5-OCH ₃		2 6	6-OCH ₃	
2 2	5-OCH ₃		2 7	6-OCH ₃	
2 3	5-OCH ₃		2 8	6-OCH ₃	
2 4	5-OCH ₃		2 9	6-OCH ₃	
2 5	5-OCH ₃		3 0	6-OCH ₃	

[0072]
[Table 43]

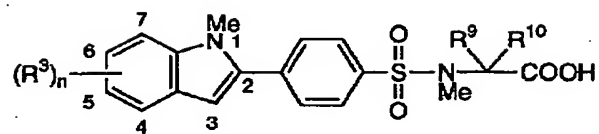
表 1 5



番号	(R ³) _n —	R ⁹ R ¹⁰	番号	(R ³) _n —	R ⁹ R ¹⁰
1	H		6	5-CH ₃	
2	H		7	5-CH ₃	
3	H		8	5-CH ₃	
4	H		9	5-CH ₃	
5	H		10	5-CH ₃	

[0073]
[Table 44]

表 15 (つづき)

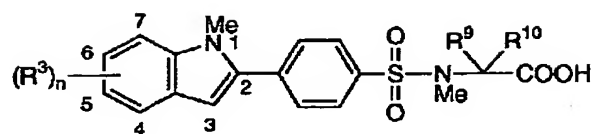


番号	(R ³) _n —	R ⁹ R ¹⁰	番号	(R ³) _n —	R ⁹ R ¹⁰
1 1	6-CH ₃		1 6	5,6-diCH ₃	
1 2	6-CH ₃		1 7	5,6-diCH ₃	
1 3	6-CH ₃		1 8	5,6-diCH ₃	
1 4	6-CH ₃		1 9	5,6-diCH ₃	
1 5	6-CH ₃		2 0	5,6-diCH ₃	

[0074]

[Table 45]

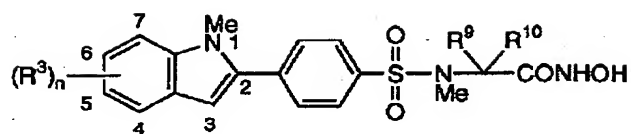
表 15 (つづき)



番号	(R ³) _n —	$\begin{array}{c} R^9 \\ \diagup \quad \diagdown \\ R^{10} \end{array}$	番号	(R ³) _n —	$\begin{array}{c} R^9 \\ \diagup \quad \diagdown \\ R^{10} \end{array}$
2 1	5-OCH ₃		2 6	6-OCH ₃	
2 2	5-OCH ₃		2 7	6-OCH ₃	
2 3	5-OCH ₃		2 8	6-OCH ₃	
2 4	5-OCH ₃		2 9	6-OCH ₃	
2 5	5-OCH ₃		3 0	6-OCH ₃	

[0075]
[Table 46]

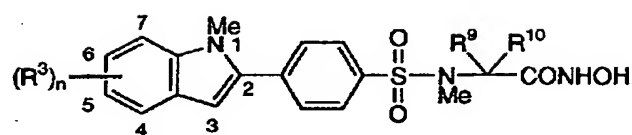
表 1 6



番号	(R ³) _n —	R ⁹ R ¹⁰	番号	(R ³) _n —	R ⁹ R ¹⁰
1	H		6	5-CH ₃	
2	H		7	5-CH ₃	
3	H		8	5-CH ₃	
4	H		9	5-CH ₃	
5	H		10	5-CH ₃	

[0076]
[Table 47]

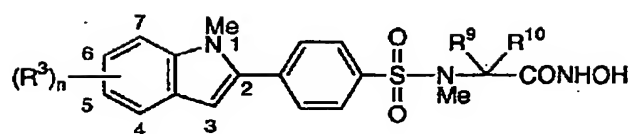
表 16 (つづき)



番号	(R ³) _n —	$\begin{array}{c} \text{R}^9 \quad \text{R}^{10} \\ \diagdown \quad \diagup \\ \text{C} \end{array}$	番号	(R ³) _n —	$\begin{array}{c} \text{R}^9 \quad \text{R}^{10} \\ \diagdown \quad \diagup \\ \text{C} \end{array}$
1 1	6-CH ₃		1 6	5,6-diCH ₃	
1 2	6-CH ₃		1 7	5,6-diCH ₃	
1 3	6-CH ₃		1 8	5,6-diCH ₃	
1 4	6-CH ₃		1 9	5,6-diCH ₃	
1 5	6-CH ₃		2 0	5,6-diCH ₃	

[0077]
[Table 48]

表 16 (つづき)

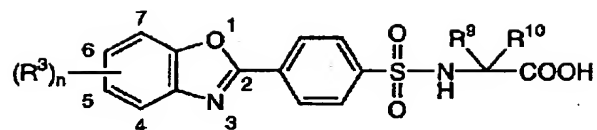


番号	(R ³) _n —	R ⁹ R ¹⁰	番号	(R ³) _n —	R ⁹ R ¹⁰
2 1	5-OCH ₃		2 6	6-OCH ₃	
2 2	5-OCH ₃		2 7	6-OCH ₃	
2 3	5-OCH ₃		2 8	6-OCH ₃	
2 4	5-OCH ₃		2 9	6-OCH ₃	
2 5	5-OCH ₃		3 0	6-OCH ₃	

[0078]

[Table 49]

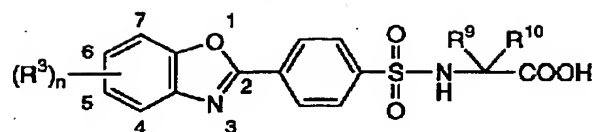
表 17



番号	(R ³) _n —	R ⁹ R ¹⁰	番号	(R ³) _n —	R ⁹ R ¹⁰
1	H		6	5-CH ₃	
2	H		7	5-CH ₃	
3	H		8	5-CH ₃	
4	H		9	5-CH ₃	
5	H		10	5-CH ₃	

[0079]
[Table 50]

表17 (つづき)

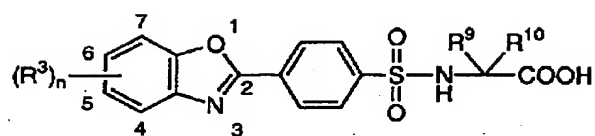


番号	(R ³) _n —	$\begin{array}{c} \text{R}^9 \quad \text{R}^{10} \\ \diagdown \quad \diagup \\ \text{C} \end{array}$	番号	(R ³) _n —	$\begin{array}{c} \text{R}^9 \quad \text{R}^{10} \\ \diagdown \quad \diagup \\ \text{C} \end{array}$
1 1	6-CH ₃		1 6	5,6-diCH ₃	
1 2	6-CH ₃		1 7	5,6-diCH ₃	
1 3	6-CH ₃		1 8	5,6-diCH ₃	
1 4	6-CH ₃		1 9	5,6-diCH ₃	
1 5	6-CH ₃		2 0	5,6-diCH ₃	

[0080]

[Table 51]

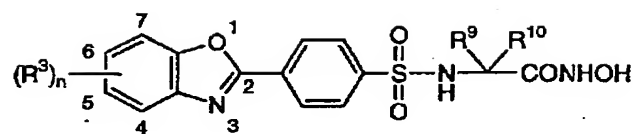
表17 (つづき)



番号	(R ³) _n —	R ⁹ R ¹⁰	番号	(R ³) _n —	R ⁹ R ¹⁰
2 1	5-OCH ₃		2 6	6-OCH ₃	
2 2	5-OCH ₃		2 7	6-OCH ₃	
2 3	5-OCH ₃		2 8	6-OCH ₃	
2 4	5-OCH ₃		2 9	6-OCH ₃	
2 5	5-OCH ₃		3 0	6-OCH ₃	

[0081]
[Table 52]

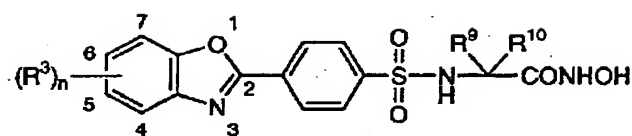
表 18



番号	(R ³) _n —	$\begin{array}{c} \text{R}^9 \quad \text{R}^{10} \\ \diagdown \quad \diagup \\ \text{C} \end{array}$	番号	(R ³) _n —	$\begin{array}{c} \text{R}^9 \quad \text{R}^{10} \\ \diagdown \quad \diagup \\ \text{C} \end{array}$
1	H		6	5-CH ₃	
2	H		7	5-CH ₃	
3	H		8	5-CH ₃	
4	H		9	5-CH ₃	
5	H		10	5-CH ₃	

[0082]
[Table 53]

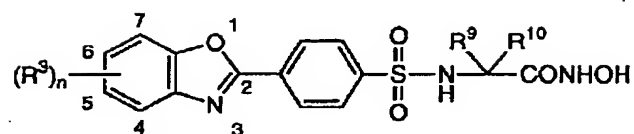
表 18 (つづき)



番号	(R ³) _n —	$\begin{array}{c} \text{R}^9 \quad \text{R}^{10} \\ \diagdown \quad \diagup \\ \text{C} \end{array}$	番号	(R ³) _n —	$\begin{array}{c} \text{R}^9 \quad \text{R}^{10} \\ \diagdown \quad \diagup \\ \text{C} \end{array}$
1 1	6-CH ₃		1 6	5,6-diCH ₃	
1 2	6-CH ₃		1 7	5,6-diCH ₃	
1 3	6-CH ₃		1 8	5,6-diCH ₃	
1 4	6-CH ₃		1 9	5,6-diCH ₃	
1 5	6-CH ₃		2 0	5,6-diCH ₃	

[0083]
[Table 54]

表18 (つづき)

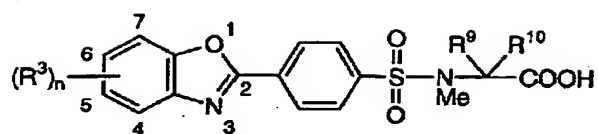


番号	(R ³) _n —	$\begin{array}{c} R^9 \\ \diagup \\ R^{10} \end{array}$	番号	(R ³) _n —	$\begin{array}{c} R^9 \\ \diagup \\ R^{10} \end{array}$
2 1	5-OCH ₃		2 6	6-OCH ₃	
2 2	5-OCH ₃		2 7	6-OCH ₃	
2 3	5-OCH ₃		2 8	6-OCH ₃	
2 4	5-OCH ₃		2 9	6-OCH ₃	
2 5	5-OCH ₃		3 0	6-OCH ₃	

[0084]

[Table 55]

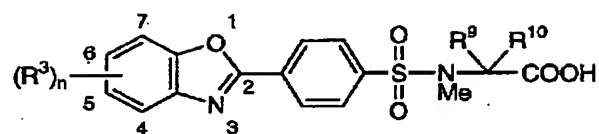
表 19



番号	(R ³) _n —	$\begin{array}{c} \text{R}^9 \quad \text{R}^{10} \\ \diagdown \quad \diagup \\ \text{C} \end{array}$	番号	(R ³) _n —	$\begin{array}{c} \text{R}^9 \quad \text{R}^{10} \\ \diagdown \quad \diagup \\ \text{C} \end{array}$
1	H		6	5-CH ₃	
2	H		7	5-CH ₃	
3	H		8	5-CH ₃	
4	H		9	5-CH ₃	
5	H		10	5-CH ₃	

[0085]
[Table 56]

表 19 (つづき)

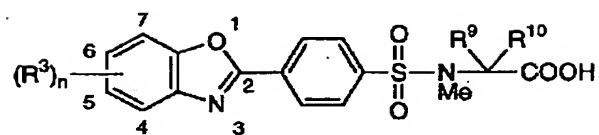


番号	(R³) _n —	$\begin{array}{c} R^9 \\ \diagup \quad \diagdown \\ R^{10} \end{array}$	番号	(R³) _n —	$\begin{array}{c} R^9 \\ \diagup \quad \diagdown \\ R^{10} \end{array}$
1 1	6-CH ₃		1 6	5,6-diCH ₃	
1 2	6-CH ₃		1 7	5,6-diCH ₃	
1 3	6-CH ₃		1 8	5,6-diCH ₃	
1 4	6-CH ₃		1 9	5,6-diCH ₃	
1 5	6-CH ₃		2 0	5,6-diCH ₃	

[0086]

[Table 57]

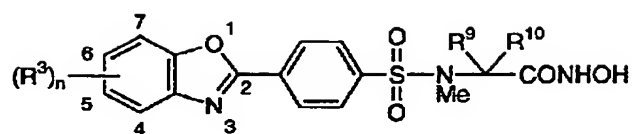
表 19 (つづき)



番号	(R ³) _n —	$\begin{array}{c} \text{R}^9 \\ \text{R}^{10} \end{array}$	番号	(R ³) _n —	$\begin{array}{c} \text{R}^9 \\ \text{R}^{10} \end{array}$
2 1	5-OCH ₃		2 6	6-OCH ₃	
2 2	5-OCH ₃		2 7	6-OCH ₃	
2 3	5-OCH ₃		2 8	6-OCH ₃	
2 4	5-OCH ₃		2 9	6-OCH ₃	
2 5	5-OCH ₃		3 0	6-OCH ₃	

[0087]
[Table 58]

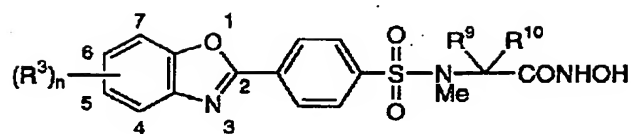
表 2 0



番号	(R ³) _n —	R ⁹ R ¹⁰	番号	(R ³) _n —	R ⁹ R ¹⁰
1	H		6	5-CH ₃	
2	H		7	5-CH ₃	
3	H		8	5-CH ₃	
4	H		9	5-CH ₃	
5	H		10	5-CH ₃	

[0088]
[Table 59]

表 20 (つづき)

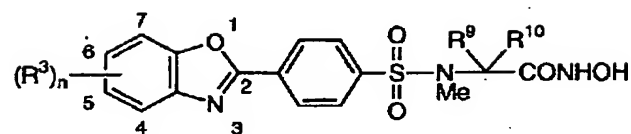


番号	(R ³) _n —	$\begin{array}{c} R^9 \\ \diagup \quad \diagdown \\ R^{10} \end{array}$	番号	(R ³) _n —	$\begin{array}{c} R^9 \\ \diagup \quad \diagdown \\ R^{10} \end{array}$
1 1	6-CH ₃		1 6	5,6-diCH ₃	
1 2	6-CH ₃		1 7	5,6-diCH ₃	
1 3	6-CH ₃		1 8	5,6-diCH ₃	
1 4	6-CH ₃		1 9	5,6-diCH ₃	
1 5	6-CH ₃		2 0	5,6-diCH ₃	

[0089]

[Table 60]

表20 (つづき)

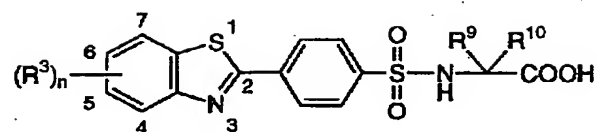


番号	(R ³) _n —	$\begin{array}{c} \text{R}^9 \quad \text{R}^{10} \\ \diagdown \quad \diagup \\ \text{C} \end{array}$	番号	(R ³) _n —	$\begin{array}{c} \text{R}^9 \quad \text{R}^{10} \\ \diagdown \quad \diagup \\ \text{C} \end{array}$
2 1	5-OCH ₃		2 6	6-OCH ₃	
2 2	5-OCH ₃		2 7	6-OCH ₃	
2 3	5-OCH ₃		2 8	6-OCH ₃	
2 4	5-OCH ₃		2 9	6-OCH ₃	
2 5	5-OCH ₃		3 0	6-OCH ₃	

[0090]

[Table 61]

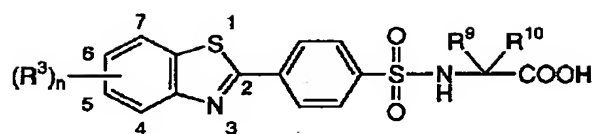
表 2 1



番号	(R ³) _n —	R ⁹ R ¹⁰	番号	(R ³) _n —	R ⁹ R ¹⁰
1	H		6	5-CH ₃	
2	H		7	5-CH ₃	
3	H		8	5-CH ₃	
4	H		9	5-CH ₃	
5	H		10	5-CH ₃	

[0091]
[Table 62]

表2 1 (つづき)

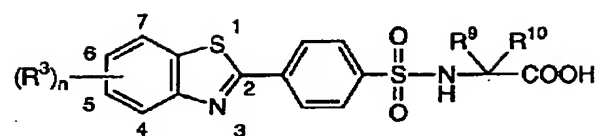


番号	(R³) _n —	$\begin{array}{c} R^9 \\ \diagup \quad \diagdown \\ R^{10} \end{array}$	番号	(R³) _n —	$\begin{array}{c} R^9 \\ \diagup \quad \diagdown \\ R^{10} \end{array}$
1 1	6-CH ₃		1 6	5,6-diCH ₃	
1 2	6-CH ₃		1 7	5,6-diCH ₃	
1 3	6-CH ₃		1 8	5,6-diCH ₃	
1 4	6-CH ₃		1 9	5,6-diCH ₃	
1 5	6-CH ₃		2 0	5,6-diCH ₃	

[0092]

[Table 63]

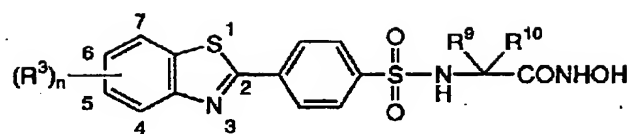
表 2 1 (つづき)



番号	(R³) _n —	$\begin{array}{c} R^9 \\ \diagup \quad \diagdown \\ R^{10} \end{array}$	番号	(R³) _n —	$\begin{array}{c} R^9 \\ \diagup \quad \diagdown \\ R^{10} \end{array}$
2 1	5-OCH ₃		2 6	6-OCH ₃	
2 2	5-OCH ₃		2 7	6-OCH ₃	
2 3	5-OCH ₃		2 8	6-OCH ₃	
2 4	5-OCH ₃		2 9	6-OCH ₃	
2 5	5-OCH ₃		3 0	6-OCH ₃	

[0093]
[Table 64]

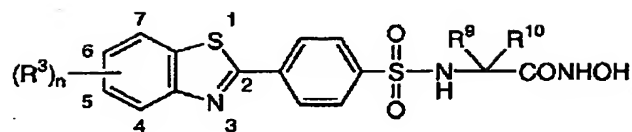
表 2 2



番号	(R ³) _n —	$\begin{matrix} R^9 & R^{10} \\ \diagdown & / \\ & C \end{matrix}$	番号	(R ³) _n —	$\begin{matrix} R^9 & R^{10} \\ \diagdown & / \\ & C \end{matrix}$
1	H		6	5-CH ₃	
2	H		7	5-CH ₃	
3	H		8	5-CH ₃	
4	H		9	5-CH ₃	
5	H		10	5-CH ₃	

[0094]
[Table 65]

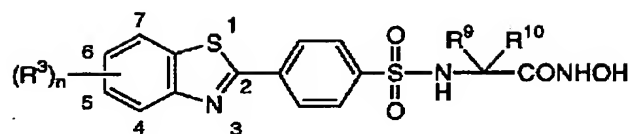
表 2 2 (つづき)



番号	(R³) _n —	R⁹ R¹⁰	番号	(R³) _n —	R⁹ R¹⁰
1 1	6-CH₃		1 6	5,6-diCH₃	
1 2	6-CH₃		1 7	5,6-diCH₃	
1 3	6-CH₃		1 8	5,6-diCH₃	
1 4	6-CH₃		1 9	5,6-diCH₃	
1 5	6-CH₃		2 0	5,6-diCH₃	

[0095]
[Table 66]

表 2 2 (つづき)

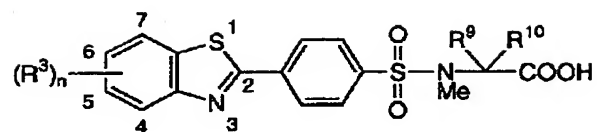


番号	(R ³) _n —	$\begin{array}{c} \text{R}^9 \quad \text{R}^{10} \\ \diagdown \quad \diagup \\ \text{CH} \end{array}$	番号	(R ³) _n —	$\begin{array}{c} \text{R}^9 \quad \text{R}^{10} \\ \diagdown \quad \diagup \\ \text{CH} \end{array}$
2 1	5-OCH ₃		2 6	6-OCH ₃	
2 2	5-OCH ₃		2 7	6-OCH ₃	
2 3	5-OCH ₃		2 8	6-OCH ₃	
2 4	5-OCH ₃		2 9	6-OCH ₃	
2 5	5-OCH ₃		3 0	6-OCH ₃	

[0096]

[Table 67]

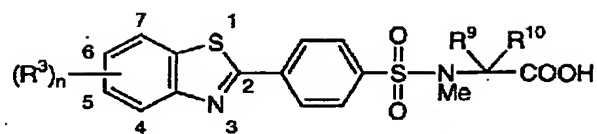
表 2 3



番号	$(R^3)_n$ —	R^9 R^{10}	番号	$(R^3)_n$ —	R^9 R^{10}
1	H		6	5-CH ₃	
2	H		7	5-CH ₃	
3	H		8	5-CH ₃	
4	H		9	5-CH ₃	
5	H		10	5-CH ₃	

[0097]
[Table 68]

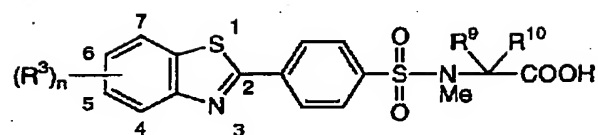
表 2 3 (つづき)



番号	(R³) _n —	R⁹ R¹⁰	番号	(R³) _n —	R⁹ R¹⁰
1 1	6-CH ₃		1 6	5,6-diCH ₃	
1 2	6-CH ₃		1 7	5,6-diCH ₃	
1 3	6-CH ₃		1 8	5,6-diCH ₃	
1 4	6-CH ₃		1 9	5,6-diCH ₃	
1 5	6-CH ₃		2 0	5,6-diCH ₃	

[0098]
[Table 69]

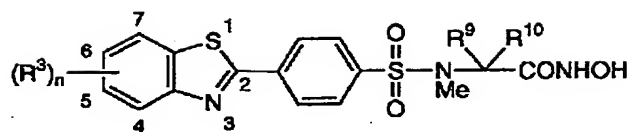
表 2 3 (つづき)



番号	(R ³) _n —	R ⁹ R ¹⁰	番号	(R ³) _n —	R ⁹ R ¹⁰
2 1	5-OCH ₃		2 6	6-OCH ₃	
2 2	5-OCH ₃		2 7	6-OCH ₃	
2 3	5-OCH ₃		2 8	6-OCH ₃	
2 4	5-OCH ₃		2 9	6-OCH ₃	
2 5	5-OCH ₃		3 0	6-OCH ₃	

[0099]
[Table 70]

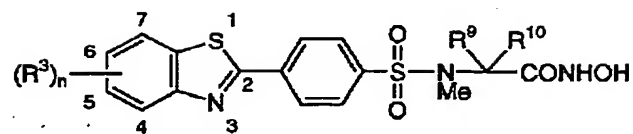
表 2 4



番号	(R ³) _n —	$\begin{array}{c} R^9 \\ \diagup \quad \diagdown \\ R^{10} \end{array}$	番号	(R ³) _n —	$\begin{array}{c} R^9 \\ \diagup \quad \diagdown \\ R^{10} \end{array}$
1	H		6	5-CH ₃	
2	H		7	5-CH ₃	
3	H		8	5-CH ₃	
4	H		9	5-CH ₃	
5	H		10	5-CH ₃	

[0100]
[Table 71]

表 2 4 (つづき)

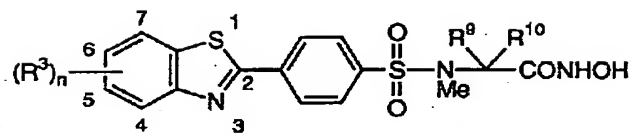


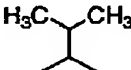
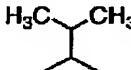


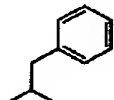
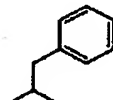
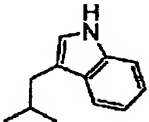
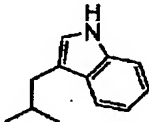
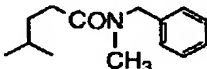

番号	(R ³) _n —	$\begin{array}{c} \text{R}^9 \quad \text{R}^{10} \\ \diagdown \quad \diagup \\ \text{C} \end{array}$	番号	(R ³) _n —	$\begin{array}{c} \text{R}^9 \quad \text{R}^{10} \\ \diagdown \quad \diagup \\ \text{C} \end{array}$
1 1	6-CH ₃		1 6	5,6-diCH ₃	
1 2	6-CH ₃		1 7	5,6-diCH ₃	
1 3	6-CH ₃		1 8	5,6-diCH ₃	
1 4	6-CH ₃		1 9	5,6-diCH ₃	
1 5	6-CH ₃		2 0	5,6-diCH ₃	

[0101]

[Table 72]

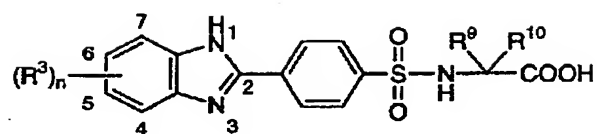
表24 (つづき)



番号	$(R^3)_n-$	$\underline{R^9} \quad \underline{R^{10}}$	番号	$(R^3)_n-$	$\underline{R^9} \quad \underline{R^{10}}$
2 1	5-OCH ₃		2 6	6-OCH ₃	
2 2	5-OCH ₃		2 7	6-OCH ₃	
2 3	5-OCH ₃		2 8	6-OCH ₃	
2 4	5-OCH ₃		2 9	6-OCH ₃	
2 5	5-OCH ₃		3 0	6-OCH ₃	

[0102]
[Table 73]

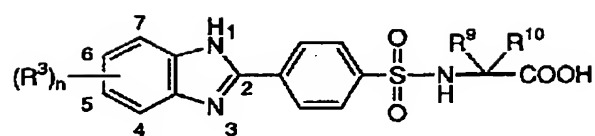
表 2 5



番号	(R³) _n —	R⁹ R¹⁰	番号	(R³) _n —	R⁹ R¹⁰
1	H		6	5-CH ₃	
2	H		7	5-CH ₃	
3	H		8	5-CH ₃	
4	H		9	5-CH ₃	
5	H		10	5-CH ₃	

[0103]
[Table 74]

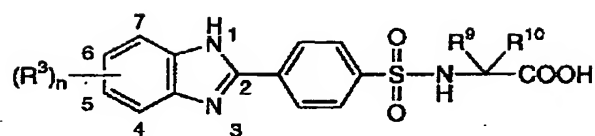
表 2 5 (つづき)



番号	(R ³) _n —	R ⁹ R ¹⁰	番号	(R ³) _n —	R ⁹ R ¹⁰
1 1	6-CH ₃		1 6	5,6-diCH ₃	
1 2	6-CH ₃		1 7	5,6-diCH ₃	
1 3	6-CH ₃		1 8	5,6-diCH ₃	
1 4	6-CH ₃		1 9	5,6-diCH ₃	
1 5	6-CH ₃		2 0	5,6-diCH ₃	

[0104]
[Table 75]

表 2 5 (つづき)

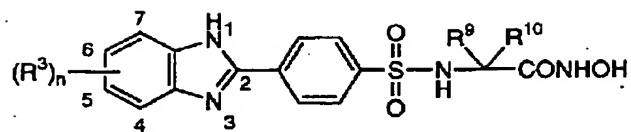


番号	(R ³) _n —	$\begin{array}{c} R^9 \\ \diagup \quad \diagdown \\ R^{10} \end{array}$	番号	(R ³) _n —	$\begin{array}{c} R^9 \\ \diagup \quad \diagdown \\ R^{10} \end{array}$
2 1	5-OCH ₃		2 6	6-OCH ₃	
2 2	5-OCH ₃		2 7	6-OCH ₃	
2 3	5-OCH ₃		2 8	6-OCH ₃	
2 4	5-OCH ₃		2 9	6-OCH ₃	
2 5	5-OCH ₃		3 0	6-OCH ₃	

[0105]

[Table 76]

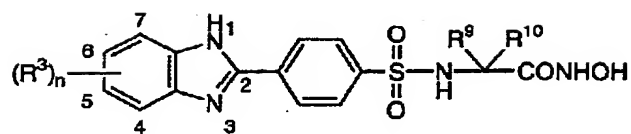
表 2 6



番号	(R³) _n —	$\begin{array}{c} \text{R}^9 \quad \text{R}^{10} \\ \diagdown \quad \diagup \\ \text{C} \end{array}$	番号	(R³) _n —	$\begin{array}{c} \text{R}^9 \quad \text{R}^{10} \\ \diagdown \quad \diagup \\ \text{C} \end{array}$
1	H		6	5-CH ₃	
2	H		7	5-CH ₃	
3	H		8	5-CH ₃	
4	H		9	5-CH ₃	
5	H		10	5-CH ₃	

[0106]
[Table 77]

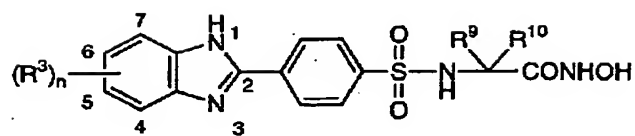
表 2 6 (つづき)



番号	(R ³) _n —	R ⁹ R ¹⁰	番号	(R ³) _n —	R ⁹ R ¹⁰
1 1	6-CH ₃		1 6	5,6-diCH ₃	
1 2	6-CH ₃		1 7	5,6-diCH ₃	
1 3	6-CH ₃		1 8	5,6-diCH ₃	
1 4	6-CH ₃		1 9	5,6-diCH ₃	
1 5	6-CH ₃		2 0	5,6-diCH ₃	

[0107]
[Table 78]

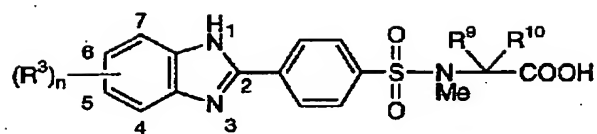
表 2 6 (つづき)



番号	(R ³) _n —	$\begin{array}{c} \text{R}^9 \quad \text{R}^{10} \\ \diagdown \quad \diagup \\ \text{C} \end{array}$	番号	(R ³) _n —	$\begin{array}{c} \text{R}^9 \quad \text{R}^{10} \\ \diagdown \quad \diagup \\ \text{C} \end{array}$
2 1	5-OCH ₃		2 6	6-OCH ₃	
2 2	5-OCH ₃		2 7	6-OCH ₃	
2 3	5-OCH ₃		2 8	6-OCH ₃	
2 4	5-OCH ₃		2 9	6-OCH ₃	
2 5	5-OCH ₃		3 0	6-OCH ₃	

[0108]
[Table 79]

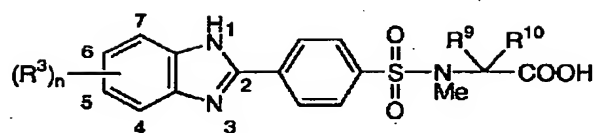
表 2 7



番号	(R ³) _n —	R ⁹ R ¹⁰	番号	(R ³) _n —	R ⁹ R ¹⁰
1	H		6	5-CH ₃	
2	H		7	5-CH ₃	
3	H		8	5-CH ₃	
4	H		9	5-CH ₃	
5	H		10	5-CH ₃	

[0109]
[Table 80]

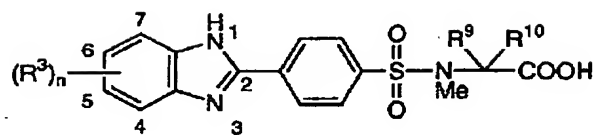
表27 (つづき)



番号	(R ³) _n —	R ⁹ R ¹⁰	番号	(R ³) _n —	R ⁹ R ¹⁰
1 1	6-CH ₃		1 6	5,6-diCH ₃	
1 2	6-CH ₃		1 7	5,6-diCH ₃	
1 3	6-CH ₃		1 8	5,6-diCH ₃	
1 4	6-CH ₃		1 9	5,6-diCH ₃	
1 5	6-CH ₃		2 0	5,6-diCH ₃	

[0110]
[Table 81]

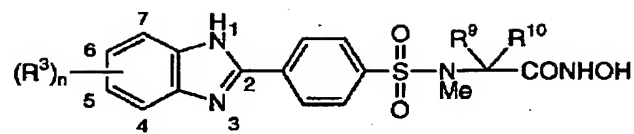
表 2 7 (つづき)



番号	(R ³) _n —	$\begin{array}{c} \text{R}^9 \quad \text{R}^{10} \\ \diagdown \quad \diagup \\ \text{C} \end{array}$	番号	(R ³) _n —	$\begin{array}{c} \text{R}^9 \quad \text{R}^{10} \\ \diagdown \quad \diagup \\ \text{C} \end{array}$
2 1	5-OCH ₃		2 6	6-OCH ₃	
2 2	5-OCH ₃		2 7	6-OCH ₃	
2 3	5-OCH ₃		2 8	6-OCH ₃	
2 4	5-OCH ₃		2 9	6-OCH ₃	
2 5	5-OCH ₃		3 0	6-OCH ₃	

[0111]
[Table 82]

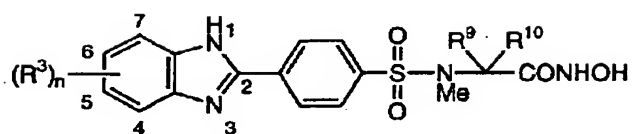
表 2 8



番号	(R ³) _n —	R ⁹ R ¹⁰	番号	(R ³) _n —	R ⁹ R ¹⁰
1	H		6	5-CH ₃	
2	H		7	5-CH ₃	
3	H		8	5-CH ₃	
4	H		9	5-CH ₃	
5	H		10	5-CH ₃	

[0112]
[Table 83]

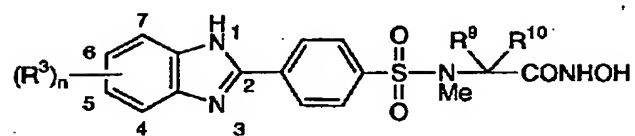
表 28 (つづき)



番号	(R ³) _n —	$\begin{array}{c} R^9 \\ \diagup \quad \diagdown \\ R^{10} \end{array}$	番号	(R ³) _n —	$\begin{array}{c} R^9 \\ \diagup \quad \diagdown \\ R^{10} \end{array}$
1 1	6-CH ₃		1 6	5,6-diCH ₃	
1 2	6-CH ₃		1 7	5,6-diCH ₃	
1 3	6-CH ₃		1 8	5,6-diCH ₃	
1 4	6-CH ₃		1 9	5,6-diCH ₃	
1 5	6-CH ₃		2 0	5,6-diCH ₃	

[0113]
[Table 84]

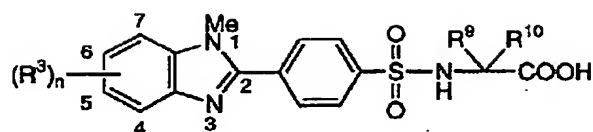
表 2 8 (つづき)



番号	(R ³) _n —	$\begin{array}{c} \text{R}^9 \quad \text{R}^{10} \\ \diagdown \quad / \\ \text{C} \end{array}$	番号	(R ³) _n —	$\begin{array}{c} \text{R}^9 \quad \text{R}^{10} \\ \diagdown \quad / \\ \text{C} \end{array}$
2 1	5-OCH ₃		2 6	6-OCH ₃	
2 2	5-OCH ₃		2 7	6-OCH ₃	
2 3	5-OCH ₃		2 8	6-OCH ₃	
2 4	5-OCH ₃		2 9	6-OCH ₃	
2 5	5-OCH ₃		3 0	6-OCH ₃	

[0114]
[Table 85]

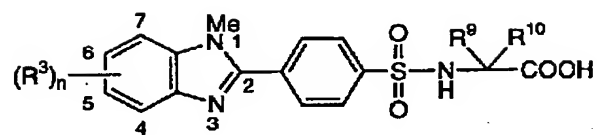
表 2 9



番号	(R ³) _n —	R ⁹ R ¹⁰	番号	(R ³) _n —	R ⁹ R ¹⁰
1	H		6	5-CH ₃	
2	H		7	5-CH ₃	
3	H		8	5-CH ₃	
4	H		9	5-CH ₃	
5	H		10	5-CH ₃	

[0115]
[Table 86]

表 2 9 (つづき)

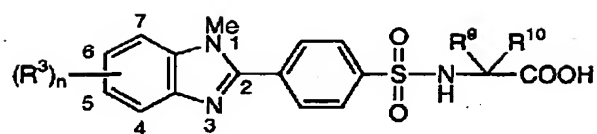


番号	$(R^3)_n$ —	R^9 R^{10}	番号	$(R^3)_n$ —	R^9 R^{10}
1 1	6-CH ₃		1 6	5,6-diCH ₃	
1 2	6-CH ₃		1 7	5,6-diCH ₃	
1 3	6-CH ₃		1 8	5,6-diCH ₃	
1 4	6-CH ₃		1 9	5,6-diCH ₃	
1 5	6-CH ₃		2 0	5,6-diCH ₃	

[0116]

[Table 87]

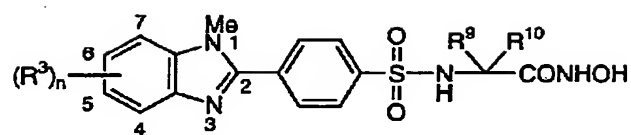
表 2 9 (つづき)



番号	(R ³) _n —	R ⁹ R ¹⁰	番号	(R ³) _n —	R ⁹ R ¹⁰
2 1	5-OCH ₃		2 6	6-OCH ₃	
2 2	5-OCH ₃		2 7	6-OCH ₃	
2 3	5-OCH ₃		2 8	6-OCH ₃	
2 4	5-OCH ₃		2 9	6-OCH ₃	
2 5	5-OCH ₃		3 0	6-OCH ₃	

[0117]
[Table 88]

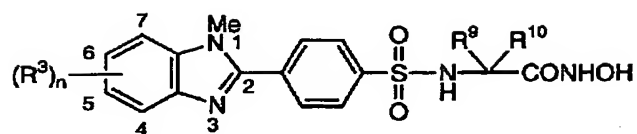
表 3 0



番号	(R ³) _n —	R ⁹ R ¹⁰	番号	(R ³) _n —	R ⁹ R ¹⁰
1	H		6	5-CH ₃	
2	H		7	5-CH ₃	
3	H		8	5-CH ₃	
4	H		9	5-CH ₃	
5	H		10	5-CH ₃	

[0118]
[Table 89]

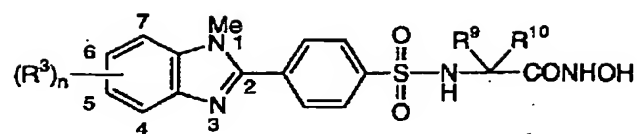
表30 (つづき)



番号	(R ³) _n —	R ⁹ R ¹⁰	番号	(R ³) _n —	R ⁹ R ¹⁰
1 1	6-CH ₃		1 6	5,6-diCH ₃	
1 2	6-CH ₃		1 7	5,6-diCH ₃	
1 3	6-CH ₃		1 8	5,6-diCH ₃	
1 4	6-CH ₃		1 9	5,6-diCH ₃	
1 5	6-CH ₃		2 0	5,6-diCH ₃	

[0119]
[Table 90]

表 30 (つづき)

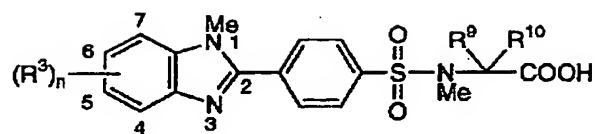


番号	(R ³) _n —	R ⁹ R ¹⁰	番号	(R ³) _n —	R ⁹ R ¹⁰
2 1	5-OCH ₃		2 6	6-OCH ₃	
2 2	5-OCH ₃		2 7	6-OCH ₃	
2 3	5-OCH ₃		2 8	6-OCH ₃	
2 4	5-OCH ₃		2 9	6-OCH ₃	
2 5	5-OCH ₃		3 0	6-OCH ₃	

[0120]

[Table 91]

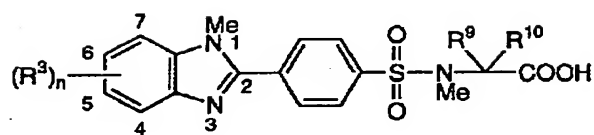
表 3 1



番号	(R ³) _n —	R ⁹ R ¹⁰	番号	(R ³) _n —	R ⁹ R ¹⁰
1	H		6	5-CH ₃	
2	H		7	5-CH ₃	
3	H		8	5-CH ₃	
4	H		9	5-CH ₃	
5	H		10	5-CH ₃	

[0121]
[Table 92]

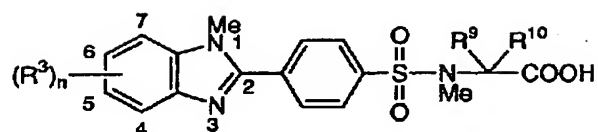
表 3 1 (つづき)



番号	(R ³) _n —	R ⁹ R ¹⁰	番号	(R ³) _n —	R ⁹ R ¹⁰
1 1	6-CH ₃		1 6	5,6-diCH ₃	
1 2	6-CH ₃		1 7	5,6-diCH ₃	
1 3	6-CH ₃		1 8	5,6-diCH ₃	
1 4	6-CH ₃		1 9	5,6-diCH ₃	
1 5	6-CH ₃		2 0	5,6-diCH ₃	

[0122]
[Table 93]

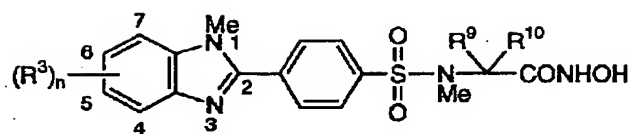
表 3 1 (つづき)



番号	(R ³) _n —	R ⁹ R ¹⁰	番号	(R ³) _n —	R ⁹ R ¹⁰
2 1	5-OCH ₃		2 6	6-OCH ₃	
2 2	5-OCH ₃		2 7	6-OCH ₃	
2 3	5-OCH ₃		2 8	6-OCH ₃	
2 4	5-OCH ₃		2 9	6-OCH ₃	
2 5	5-OCH ₃		3 0	6-OCH ₃	

[0123]
[Table 94]

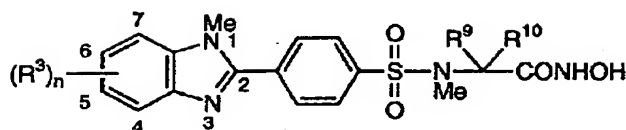
表 3 2



番号	(R ³) _n —	$\begin{array}{c} \text{R}^9 \quad \text{R}^{10} \\ \diagdown \quad \diagup \\ \text{C} \end{array}$	番号	(R ³) _n —	$\begin{array}{c} \text{R}^9 \quad \text{R}^{10} \\ \diagdown \quad \diagup \\ \text{C} \end{array}$
1	H		6	5-CH ₃	
2	H		7	5-CH ₃	
3	H		8	5-CH ₃	
4	H		9	5-CH ₃	
5	H		10	5-CH ₃	

[0124]
[Table 95]

表 3 2 (つづき)



番号	(R ³) _n —	R ⁹ R ¹⁰	番号	(R ³) _n —	R ⁹ R ¹⁰
2 1	5-OCH ₃		2 6	6-OCH ₃	
2 2	5-OCH ₃		2 7	6-OCH ₃	
2 3	5-OCH ₃		2 8	6-OCH ₃	
2 4	5-OCH ₃		2 9	6-OCH ₃	
2 5	5-OCH ₃		3 0	6-OCH ₃	

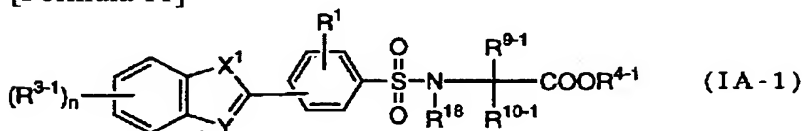
[0126]

[Methods for Producing the Invented Chemical Compound]this invention compound shown by general formula (I) can be manufactured by the method indicated in the following methods or examples.

(1) R² can manufacture the compound which is COOR⁴ by the method of of the following (a) or (b) among this invention compounds shown by general formula (I).

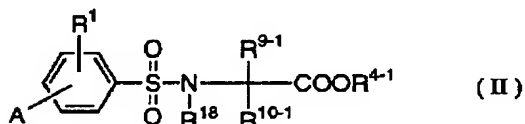
(a) Neither R³ nor R⁹ nor R¹⁰ group nor the COOR⁴ group in R² expresses the basis containing - COOH group or it, And the thing [any] group of R³, R⁹, and R¹⁰ group does not express the basis containing a hydroxyl group or it, (And the compound in which the thing [any] group of R³, X, R⁹, and R¹⁰ group does not express the basis containing an amino group or it, i.e., a general formula, (IA-1))

[Formula 11]

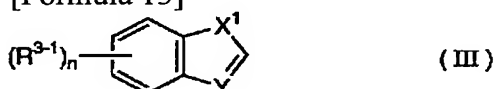


the inside of a formula, and R⁴⁻¹ -- C1 - 8 alkyl groups, a phenyl group, or a phenyl group. - An OCOR⁶ group (R⁶ expresses the same meaning as the above among a basis.), or a -CONR⁷R⁸ group (among a basis) R⁷ and R⁸ express the same meaning as the above. C1 replaced - 4 alkyl groups are expressed. Although it expresses and X¹

expresses the same meaning as X, Although the amino group in X^1 expresses the protected amino group and R^{3-1} , R^{9-1} , and R^{10-1} express the respectively same meaning as R^3 , R^9 , and R^{10} . The inside of R^{3-1} , R^{9-1} , and R^{10-1} group, - COOH group, The basis containing a hydroxyl group, an amino group, or them expresses the basis containing the protected bases or those bases that were protected, respectively, and other signs express the same meaning as the above. The compound shown is general formula (II). [Formula 12]



(A expresses a halogen atom or a trifluoromethane sulfonyloxy group among a formula, and other signs express the same meaning as the above.) -- the compound shown and general formula (III) [Formula 13]

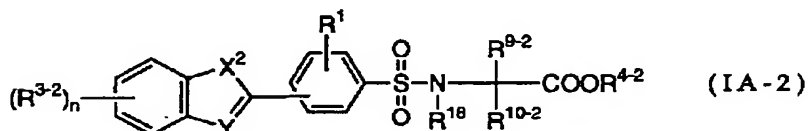


(all the signs express the same meaning as the above among a formula.) -- it can manufacture by making the compound shown react.

[0127]The reaction with the condensed heterocyclic compound shown by the compound which is general formula (II) and is shown, and general formula (III) is publicly known, for example, the inside (tetrahydrofuran etc.) of an organic solvent and alkyl lithium (n-butyl lithium.) Under existence of halogenation metal (zinc chloride, a magnesium chloride, or trialkyltin chloride (trimethyl tin chloride)), such as t-butyl lithium, It can manufacture by making it react at 0-100 ** using catalysts (tetrakis (triphenyl phosphine) palladium etc.).

[0128](b) The basis of either R^3 , R^9 , R^{10} group and the $COOR^4$ group in R^2 . [whether the basis containing - COOH group or it is expressed, and] Or the basis of either R^3 , R^9 and R^{10} group. [whether the basis containing a hydroxyl group or it is expressed, and] (Or the compound showing the basis on which the basis of either R^3 , X , R^9 and R^{10} group contains an amino group or it, i.e., a general formula, (IA-2))

[Formula 14]



(Among a formula, although the respectively same meaning as R^3 , X , R^4 , R^9 , and R^{10} is expressed, R^{3-2} , X^2 , R^{4-2} , R^{9-2} , and R^{10-2}) At least one basis among R^{3-2} , X^2 , a - $COOR^{4-2}$ group, R^{9-2} , and R^{10-2} - COOH group, Expressing the basis containing a hydroxyl group, an amino group, or them, other signs express the same meaning as the above. The compound shown can be manufactured by giving the compound shown by a general formula (IA-1) to the deprotection reaction under alkali hydrolysis or acid conditions.

[0129]the deprotection reaction by alkali hydrolysis is publicly known -- for example, an organic solvent (methanol.) hydroxide (sodium hydroxide.) of inside and alkaline

metals, such as a tetrahydrofuran and dioxane A potassium hydrate, lithium hydroxide, etc. are performed at the temperature of 0-40 ** using hydroxide (calcium hydroxide etc.), carbonate (sodium carbonate, potassium carbonate, etc.), the solution of those, or these mixtures of alkaline-earth metals. the deprotection reaction under acid conditions is also publicly known -- for example, an organic solvent (a methylene chloride.) It is carried out at the temperature of 0-90 ** into chloroform, dioxane, ethyl acetate, an anisole, etc. among organic acid (trifluoroacetic acid, methanesulfonic acid, iodination trimethylsilyl, etc.), inorganic acid (chloride etc.), or these mixtures (hydrogen bromide acetic acid etc.).

[0130]The ester compound which carries out considerable can be manufactured by giving the compound which has at least one - COOH group among the compounds shown by a general formula (IA-2) to an esterification reaction. The esterification reaction is publicly known, for example, the method of using (1) diazoalkane, the method of using (2) alkyl halide, the method of using a (3) dimethylformamide (DMF)-dialkyl acetal, the method of making it react to alkanol (4) Corresponding, etc. are mentioned.

[0131]If these methods are explained concretely, the method of using (1) diazoalkane, For example, it is carried out by making it react at -10 **-40 ** using corresponding diazoalkane among an organic solvent (diethylether, ethyl acetate, a methylene chloride, acetone, methanol, ethanol, etc.).

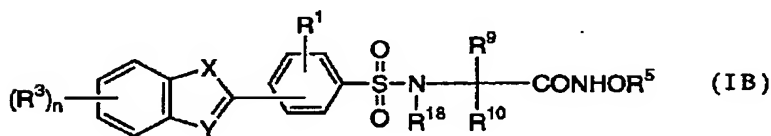
(2) the method of using alkyl halide -- an organic solvent (acetone.) It is carried out into DMF, dimethyl sulfoxide (DMSO), etc. using corresponding alkyl halide by making it react at -10 ** - 40 ** under existence of bases (potassium carbonate, sodium carbonate, potassium bicarbonate, sodium bicarbonate, a calcium oxide, etc.).

(3) The method of using a DMF-dialkyl acetal is performed, for example among an organic solvent (benzene, toluene, etc.) using a corresponding DMF-dialkyl acetal by making it react at -10 ** - 40 **.

(4) The method of making it react to corresponding alkanol, for example, the inside of corresponding alkanol and acid (chloride, sulfuric acid, and p-toluenesulfonic acid.) It is carried out by making it react at 0-40 ** using condensing agents (1,3-dicyclohexylcarbodiimide (DCC), pivaloyl halide, aryl sulfonyl halide, alkyl sulfonyl halide, etc.), such as hydrogen chloride gas. Of course, these esterification reactions may add the organic solvents (a tetrahydrofuran, a methylene chloride, etc.) which do not participate in a reaction, and may be performed.

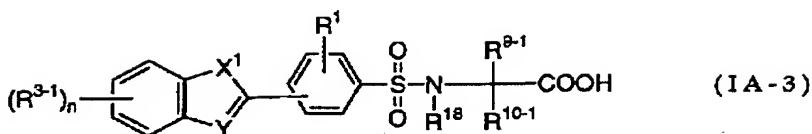
[0132]((2) The compound (IB), i.e., the general formula, whose R^2 is CONHOR⁵ among this invention compounds shown by general formula (I))

[Formula 15]



(all the signs express the same meaning as the above among a formula.) ---the compound shown -- general formula (IA-3)

[Formula 16]



(all the signs express the same meaning as the above among a formula.) -- the compound shown and general formula (IV)

[Formula 17] $\text{NH}_2\text{OR}^{5-1}$ (IV)

the inside of a formula, and R^{5-1} -- a hydrogen atom, C1 - 8 alkyl groups, and a phenyl group. Or C1 replaced by the phenyl group - 4 alkyl groups, or the protective group of the other hydroxylamine. (For example, $-\text{C}(\text{CH}_3)_2\text{OCH}_3$, a t-butoxycarbonyl group, or a benzyloxycarbonyl group) etc. is expressed. It can manufacture by giving an amidation reaction with the compound shown. If required, it can also manufacture by giving the hydrolysis under alkali conditions, and/or the deprotection reaction under acid conditions succeedingly.

[0133] The amidation reaction in which make amine react to acid and an amide bond is made to form is publicly known, for example, the method of using (1) acid halide, the method of using (2) mixed acid anhydrides, the method of using (3) condensing agents, etc. are mentioned.

[0134] If these methods are explained concretely, the method of using (1) acid halide, For example, carboxylic acid with the inside (chloroform, a methylene chloride, diethylether, a tetrahydrofuran, etc.) of an organic solvent, or a non-solvent. It is made to react to acid halide (oxalyl chloride, thionyl chloride, etc.) at -20°C - flowing-back temperature, It is carried out by making the obtained acid halide react to amine at $0-40^\circ\text{C}$ among an organic solvent (chloroform, a methylene chloride, diethylether, a tetrahydrofuran, etc.) under existence of the third class amine (pyridine, triethylamine, dimethylaniline, dimethylamino pyridine, etc.).

[0135] (2) The methods of using a mixed acid anhydride are inside (chloroform, a methylene chloride, diethylether, a tetrahydrofuran, etc.) of an organic solvent, or a non-solvent about carboxylic acid, for example, Under existence of the third class amine (pyridine, triethylamine, dimethylaniline, dimethylamino pyridine, etc.), Acid halide (a pivaloyl chloride, tosyl chloride, mesyl chloride, etc.). Or it is carried out by making it react to acid derivatives (ethyl chloroformate, KUROROGI acid isobutyl, etc.) at $0-40^\circ\text{C}$, and making the mixed acid anhydride and amine which were obtained react at $0-40^\circ\text{C}$ among an organic solvent (chloroform, a methylene chloride, diethylether, a tetrahydrofuran, etc.).

[0136] (3) The method of using a condensing agent is a non-solvent about carboxylic acid and amine, for example among an organic solvent (chloroform, a methylene chloride, dimethylformamide, diethylether, a tetrahydrofuran, etc.), Under existence of the third class amine (pyridine, triethylamine, dimethylaniline, dimethylamino pyridine, etc.) or nonexistence, a condensing agent (1,3-dicyclohexylcarbodiimide (DCC) and 1-ethyl-3-[3-(dimethylamino) propyl] carbodiimide (EDC).) It is carried out by making it react at $0-40^\circ\text{C}$ without using whether 1-hydroxybenztriazole (HOBt) is used using 1,1'-carbonyldiimidazole (CDI), 2-chloro-1-methylpyridinium iodine, etc. As for each of reactions of these (1), (2), and (3), it is desirable under inactive gas (argon, nitrogen, etc.) atmosphere to carry out on anhydrous conditions.

[0137] A deprotection reaction means the deprotection reaction under the general deprotection reaction which a person skilled in the art can understand easily, for example, alkali hydrolysis, and acid conditions, and this invention compound made

into the purpose is easily manufactured by using these reactions properly. Deprotection under alkali hydrolysis and acid conditions can be performed by the same method as the above.

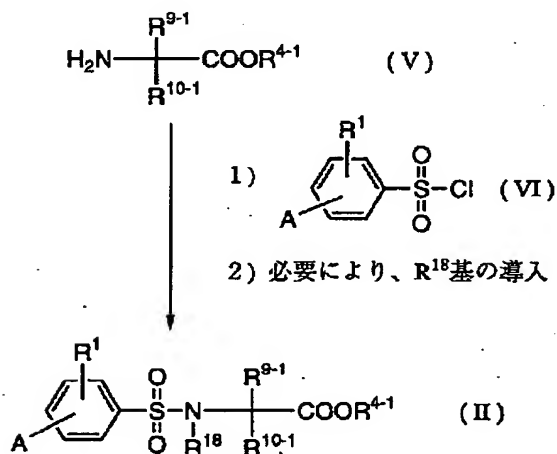
[0138] Although it is that a person skilled in the art can understand easily, and t-butyl group and benzyl are mentioned as a protective group of a carboxyl group and a hydroxyl group, it will not be limited especially if it is a basis from which it can be desorbed easily and selectively besides it. For example What was indicated to T. W. Greene, Protective Groups in Organic Synthesis, Wiley, New York, and 1991 is used. As a protective group of an amino group, although a benzyloxycarbonyl group and a t-butoxycarbonyl group are mentioned, especially if it is a basis from which it can be desorbed easily and selectively besides it, it will not be limited. For example, $-\text{C}(\text{CH}_3)_2\text{OCH}_3$ etc. are used. this invention compound made into the purpose is easily manufactured by using these protective groups properly. It will not be limited especially if it is a basis from which it can be desorbed easily and selectively besides t-butyl group and benzyl as a protective group of hydroxylamine. For example, $-\text{C}(\text{CH}_3)_2\text{OCH}_3$, a t-butoxycarbonyl group, or a benzyloxycarbonyl group is used. this invention compound made into the purpose is easily manufactured by using these protective groups properly.

[0139] The compound shown by general formula (II) can be manufactured by the method shown by the publicly known method or the following reaction process type 1. A series of reactions are shown in the following reaction process types 2 and 3.

[0140]

[Formula 18]

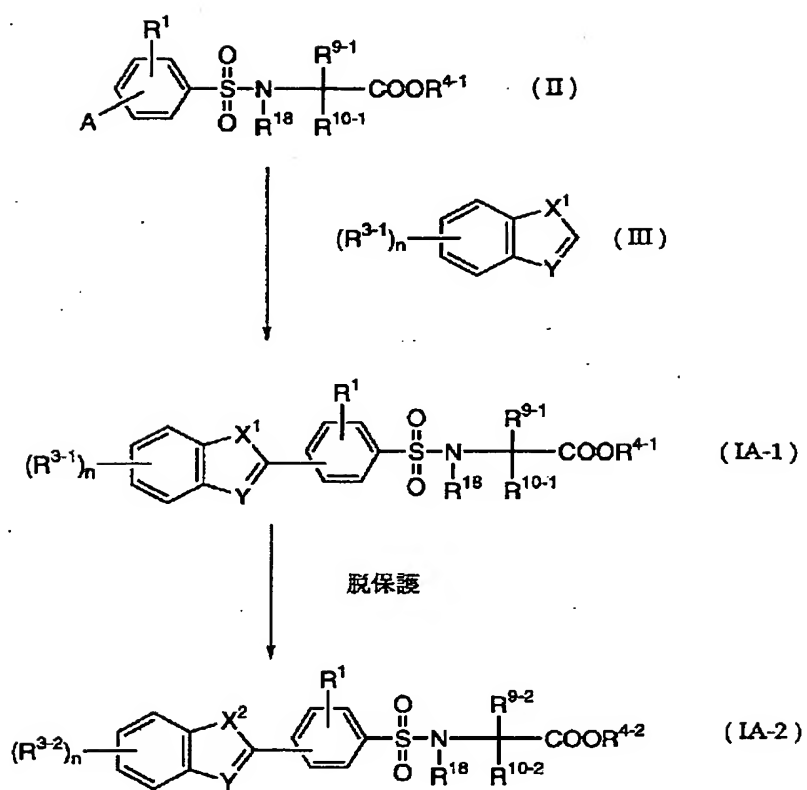
反応工程式1



[0141]

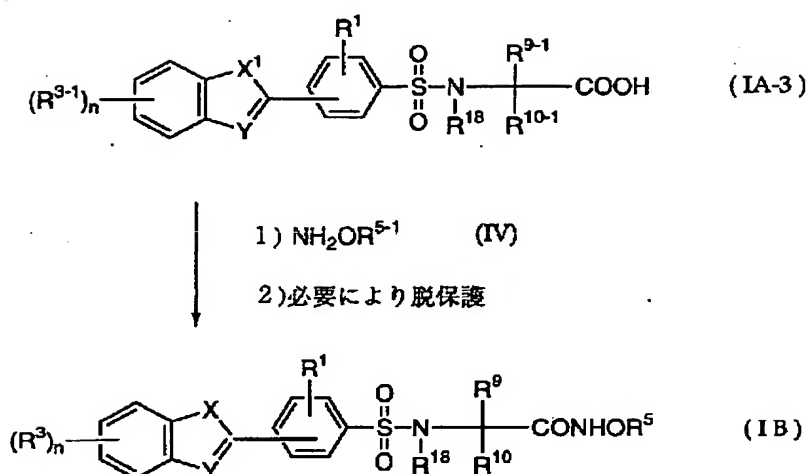
[Formula 19]

反応工程式 2



[0142]
[Formula 20]

反応工程式 3



[0143]The compound shown by general formula (IV), general formula (V), or general formula (VI) used as a starting material is publicly known in itself, or can be easily manufactured by a publicly known method. Other starting material and each reagent (for example, compound shown by general formula (III)) in this invention are publicly known in itself, or can be manufactured by a publicly known method.

[0144]In each reaction in this specification, a refining means usual in a resultant. For example, it can refine by methods using the distillation under ordinary pressure or decompression, silica gel, or a magnesium silicate, such as high performance chromatography, thin layer chromatography, column chromatography or washing, and recrystallization. Refining may be performed for every reaction and it may carry out after some ending reaction.

[0145]

[Pharmacological activity] The following experiments proved that this invention compound shown by general formula (I) has matrix metalaw proteinase inhibiting activity.

[0146](1) the assay buffer (90microl) solution of the pro gelatinase A (7microl) refined from the gelatinase A inhibiting activity [experimental method] Homo sapiens normal dermal fibroblast (HNDF) -- p-aminophenyl mercury acetate (APMA) (10microl) of 10mM -- in addition, Preincubation was carried out at 37 ** for 1 hour, and the enzyme was activated. The solution (10microl) which does not add the solution of a test compound or test compound of a synthetic substrate (MOCac-Pro-Leu-Gly-A₂pr(Dnp)-Ala-Arg-NH₂) (890microl; last concentration 13.5microM) and various concentration. Preincubation was carried out for 5 minutes at 37 **. the activating enzyme (7microl/tube, 100microl) prepared above there -- in addition, the incubation was carried out for 20 minutes at 37 **, after that, the 0.1M sodium acetate buffer (2ml;pH4.0) was added, and the enzyme reaction was stopped. Gelatinase activity was computed by measuring the fluorescence intensity (Ex=328nm and Em = 393 nm) of a reaction solution. A result is shown in Table 33.

[0147]

[Table 97]

表 3 3

实施例番号	I C ₅₀ (μ M)
2	1. 8
2 (4)	1. 6
2 (6)	7. 4
2 (8)	1. 1
3	0. 3 0

[0148](2) the assay buffer (105microl) solution of pro collagenase (5microl) refined from the collagenase inhibiting activity [experimental method] Homo sapiens normal dermal fibroblast (HNDF) -- 1mg/ml of trypsin (45microl) -- in addition, Preincubation was carried out for 1 minute at 37 **, and the enzyme was activated. 5mg/ml soybean trypsin inhibitor (soybean trypsin inhibitor) (SBTI;50microl) was added in the solution, and inactivation of the trypsin was carried out to it. The solution of a test compound or test compound of a synthetic substrate (Ac-Pro-Leu-Gly-[2-mercapto-4-methyl-pentanoyl]-Leu-Gly-OEt) (105microl; last concentration 1.33mM) and various concentration. Preincubation of the solution (20microl) which is not added was carried out for 5 minutes at 26 **. the activating enzyme (75microl/tube, 50microl) prepared above there -- in addition, the incubation was carried out for 10 minutes at 26 **. The absorbance of 324 nm of a total of 40 points was measured in these 10 minutes, and Vmax in 30 points of them was made into measured value. For example, the compound of Example 2 (1) checked collagenase activity 69.3% by the concentration of 100mM.

[0149]

[Toxicity] It can be judged that the toxicity of this invention compound is very low, and it is safe enough in order to use it as medicine.

[0150]

[Application in drugs] In an animal including Homo sapiens, especially Homo sapiens, by checking matrix metalaw proteinase, for example, gelatinase, SUTOROMU lysin, or collagenase. Rheumatism, osteoarthritis, morbid osteoclasia, osteoporosis, periodontosis, the interstitial nephritis, It is useful for prevention and/or the therapy of the disease of arteriosclerosis, versicular emphysema, liver cirrhosis, cornea damage, transition permeation of a cancer cell, or growth, an autoimmune disease, the diseases (Crohn's disease, a SHUGUREN disease, etc.) by the blood vessel transmigration of the cell of a leucocyte system, or permeation, the vascularization, etc.

[0151]In order to use this invention compound shown by general formula (I), its nontoxic salt, acid addition salt, or its hydrate for the above-mentioned purpose, a medicine is usually prescribed for the patient in taking orally or a parenteral form systemic or locally. Although a dose changes with age, weight, condition, a curative effect, a medication method, processing time, etc., Usually, in 1 to [per time per one adult] 1000 mg, It is administered orally several times from 1 time per day, parenteral administration (it administers intravenously preferably) is carried out several times from 1 time per day in 1 to [per time per one adult] 100 mg, or self-sustaining

administration is carried out into a vein in 1 to [per] 24 hours day. As described above, of course, since a dose is changed by various conditions, a quantity smaller than the above-mentioned dose may be enough as it, and it may be required exceeding the range.

[0152]When prescribing this invention compound for the patient, it is used as the injections for the solid constituent for internal use, a liquid composition, other constituents, and parenteral administration, external preparations, suppositories, etc. A tablet, a pill, a capsule, powder medicine, a granule, etc. are contained in the solid constituent for internal use. A hard capsule and a soft capsule are contained in a capsule. In such a solid constituent, one or the active substance beyond it, It is mixed with one inertness diluent, for example, lactose, mannitol, glucose, hydroxypropylcellulose, microcrystalline cellulose, starch, a polyvinyl pyrrolidone, and magnesium aluminometasilicate at least. The constituent may contain a solubilizing agent like additive agents other than an inertness diluent, for example, lubricant like magnesium stearate, disintegrator like a calcium carboxymethyl cellulose, a stabilizing agent like lactose, glutamic acid, or aspartic acid in accordance with a conventional method. The tablet or the pill may be covered with the film of stomach solubility, such as white soft sugar, gelatin, hydroxypropylcellulose, and hydroxypropylmethylcellulose phthalate, or an enteric substance as occasion demands, and may be covered with two or more layers. The capsule of a substance still like gelatin by which it is absorbed and in which it deals is also included.

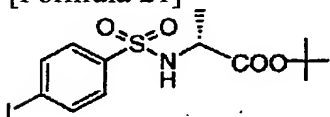
[0153]The liquid composition for internal use contains an opacifier, a solution agent, syrups, elixirs, etc. which are permitted in drugs. In such a liquid composition, one or the active substance beyond it contains in the inertness diluent (for example, purified water, ethanol) generally used. This constituent may contain a wetting agent, an adjuvant like suspension, the sweetening agent, the flavor agent, the aromatic, and the antiseptic in addition to an inertness diluent. As a constituent of others for internal use, the spray prescribed by a publicly known method in itself is contained including one or the active substance beyond it. This constituent may contain an isotonic agent like a buffer which gives stabilizer and the isotonicity like sodium hydrogen sulfite in addition to an inertness diluent, for example, sodium chloride, sodium acid citrate, or citrate. The manufacturing method of spray is *****, for example. 2,868,691 It is indicated in detail in an item and the 3,095,355th item.

[0154]As injections for the parenteral administration by this invention, a sterile water or non-aqueous solution agent, suspension, and an opacifier are included. As a water solution agent and suspension, distilled water for injection and a physiological saline are contained, for example. As the solution agent of nonaqueous solubility, and suspension, there are propylene glycol, a polyethylene glycol, vegetable oil like olive oil, alcohols like ethanol, polysorbate 80 (registered trademark), etc., for example. Such a constituent may contain an adjuvant still like an antiseptic, a wetting agent, an emulsifier, a dispersing agent, a stabilizing agent (for example, lactose), and a solubilizing agent (for example, glutamic acid, aspartic acid). These are sanitized by the combination or the exposure of filtration and a germicide which lets a bacteria suspension filter pass. These manufacture a sterile solid constituent again, for example, they can also use it for sanitization, sterile distilled water for injection, or other solvents before use of a freeze-drying article, dissolving. As a constituent of others for parenteral administration, the pessary for the suppositories for the outside solution agent prescribed by a conventional method, ointment, the paint, and intrarectal administration and the administration in a vagina, etc. are contained including one or the active substance beyond it.

[0155]

[Example] Hereafter, although this invention is explained in full detail according to a reference example and an example, this invention is not limited to these. The solvent in the parenthesis shown in the part and TLC of separation by chromatography shows the used elution solvent or developing solvent, and a rate expresses a volume ratio. The solvent in the parenthesis shown in the part of NMR shows the solvent used for measurement.

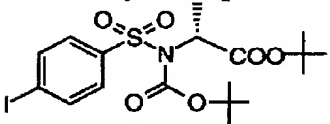
[0156] A reference example 1 N-(4-iodo phenyl sulfonyl)-D-alanine and t-butylester [Formula 21]



[0157] 4-iodobenzene sulfonyl chloride (15.1g) was gradually added to the pyridine (100 ml) solution of D-alanine and t-butylester hydrochloride (9.08g) under ice-cooling. The mixture was removed from the ice bath and it agitated at the room temperature for 1 hour. The reaction solution was condensed, and it diluted with ethyl acetate, 1N chloride, water, and a saturation salt solution washed, and it condensed after desiccation with anhydrous magnesium sulfate. Silica gel chromatography (n-hexane: ethyl acetate = 3:1 → 2:1) refined residue, and the title compound (14.3g) which has the following property value was obtained.

TLC: R_f 0.65 (n-hexane: ethyl acetate = 1:1).

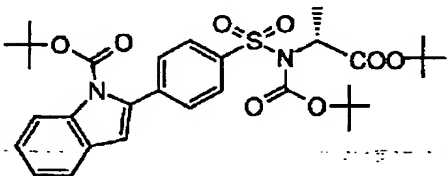
[0158] A reference example 2 N-(4-iodo phenyl sulfonyl)-N-t-carbobutoxy-D-alanine and t-butylester [Formula 22]



[0159] An N-(4-iodo phenyl sulfonyl)-D-alanine and t-butylester (it manufactured by the reference example 1.) (14g), It mixed at the room temperature and di-t-butyl dicarbonate (8g), 4-(dimethylamino) pyridine (50 mg), and acetonitrile (34 ml) were agitated for 1 hour. The reaction mixture was condensed, silica gel chromatography (n-hexane: ethyl acetate = 10:1) refined residue, and the title compound (17.1g) which has the following property value was obtained.

TLC: R_f 0.39 (n-hexane: ethyl acetate = 5:1).

[0160] An example 1 N-[[4-(1-t-butoxy KARUBONI *-*****- 2-yl) phenyl sulfonyl]] N-t-carbobutoxy-D-alanine and t-butylester [Formula 23]



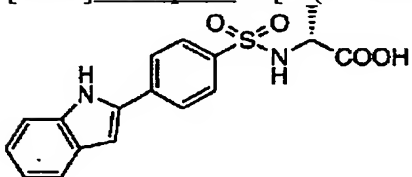
[0161] The pentane (8.8 ml) solution of t-butyl lithium of 1.5M was dropped at the tetrahydrofuran (20 ml) solution of N-t-butoxycarbo NIRUINDORU (2.61g) during the dry ice methanol bath, and was agitated for 1 hour. The diethylether (13.2 ml) solution of zinc chloride of 1M was dropped at the mixture during the dry ice methanol bath. It is neglected until it removes reaction mixed liquor from a dry ice

methanol bath and becomes 0 **, One by one, an N-(4-iodo phenyl slufonyl)-N-t-carbobutoxy-D-alanine, t-butylester (it manufactured by the reference example 2.) (2.05g), and tetrakis (triphenyl phosphine) palladium (462 mg) were added at 0 **, and were agitated at the room temperature for 1 hour. Reaction mixed liquor was diluted with ethyl acetate, 1N chloride and saturated sodium bicarbonate solution washed, and it condensed after desiccation with anhydrous magnesium sulfate. Silica gel chromatography (n-hexane: ethyl acetate =10:1->5:1) refined residue, and the title compound (2.36g) which has the following property value was obtained.

[0162]TLC:Rf 0.34 (n-hexane: ethyl acetate =5:1);

NMR. (CD₃OD) :. delta 8.21-8.17(1H,m), 8.04(2H,d,J=8.7Hz), 7.60-7.56(1H,m), 7.57(2H,d,J=8.7Hz), 7.42-7.21(3H,m), 5.11(1H,q, J= 7.0 Hz, 1.66 (3H,d,J=7.0Hz), 1.46 (9H, s), 1.38 (18H, s).

[0163]Example 2N-[4-(2-indolyl) phenyl slufonyl]-D-alanine [Formula 24]



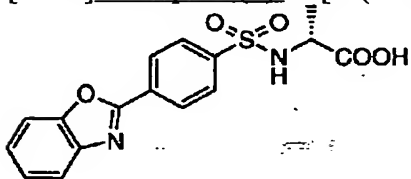
[0164]An N--[4-(1-t-butoxy KARUBONI *-*****- 2-yl) phenyl slufonyl]] N-t-carbobutoxy-D-alanine and t-butylester (it manufactured in Example 1.) (2.3g) were dissolved in trifluoroacetic acid (10 ml), and it agitated for 30 minutes at the room temperature. Diisopropyl ether washed the solid obtained by distilling off trifluoroacetic acid, it dried and the title compound (1.07g) which has the following property value was obtained.

[0165]TLC:Rf 0.18 (chloroform: methanol : acetic acid =10:1:1);

NMR. (CD₃OD) :. delta 7.94(2H,d,J=8.8Hz), 7.88(2H,d,J=8.8Hz), 7.56(1H,br.d,J=7.8Hz), 7.41(1H,br.d,J=8.0Hz), 7.14(1H,td,J=7.8, 1.2 Hz, 7.02 (1H, ddd, J= 8.0, 7.8, 1.2 Hz), 6.97 (1H, br.s), 3.94 (1H, q, J= 7.2 Hz), 1.33 (3H, d, J= 7.2 Hz).

[0166]Amino acid and t-butylester (hydrochloride) corresponding by the example 2(1)-2 (19) reference example 1 instead of D-alanine and t-butylester hydrochloride are used, The compound manufactured by the compound or the reference example 2 produced by operating it like the method shown by the reference example 1 -> reference example 2 is used, The title compound which operates it like the method shown in example 1 (heterocyclic compound corresponding instead of N-t-butoxycarbo NIRUINDORU was used.) -> example 2, and has the following property value was obtained.

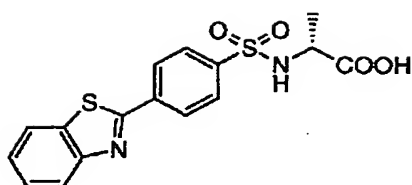
[0167]Example 2(1) N-[4-(2-benzoxazolyl) phenyl slufonyl]-D-alanine [Formula 25]



[0168]TLC:Rf 0.20 (methanol: chloroform : acetic acid : water =100:10:1:1);

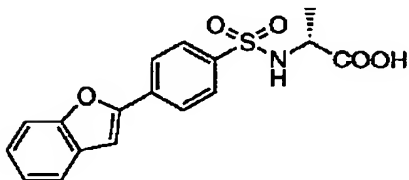
NMR. (CD₃OD) :delta J= 7.1 Hz of 8.55(2H,d,J=8.6Hz), 8.05(2H,d,J=8.6Hz), 7.8-7.7(2H,m), 7.5-7.4(2H,m), 4.01(1H,q,J=7.1Hz),1.36(3H,d,.

[0169]Example 2(2) N-[4-(2-benzothiazolyl) phenyl slufonyl]-D-alanine [Formula 26]



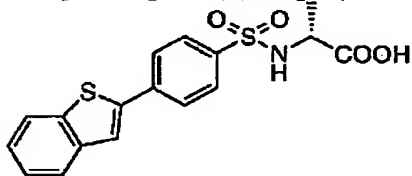
[0170]TLC:Rf 0.22 (methanol: chloroform : acetic acid : water =100:10:1:1);
NMR(CD₃OD): delta 8.26 (2H, d, J= 8.3 Hz), 8.1-8.0 (4H, m), 7.6-7.45 (2H, m), 4.00 (1H, q, J= 7.3 Hz), 1.36 (3H, d, J= 7.3 Hz).

[0171]Example 2(3) N-[4-(2-benzofuranyl) phenyl slufonyl]-D-alanine [Formula 27]



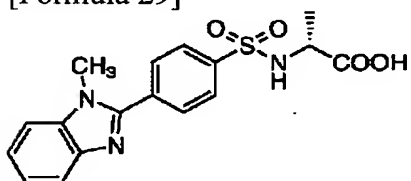
[0172]TLC:Rf 0.23 (chloroform: methanol : acetic acid =30:1:1);
NMR. (CD₃OD) :delta 8.05(2H,d,J=8.8Hz), 7.93(2H,d,J=8.8Hz), 7.67-7.53(2H,m), 7.37(1H,s), 7.38-7.21(2H,m), 3.96(1H,q,J=7.2Hz), 1.34 (3H, d, J= 7.2 Hz).

[0173]Example 2(4) N-[4-(2-benzo thienyl) phenyl slufonyl]-D-alanine [Formula 28]



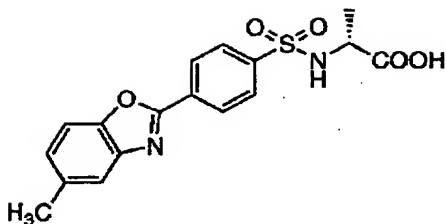
[0174]TLC:Rf 0.27 (chloroform: methanol : acetic acid =30:1:1);
NMR. (DMSO-d₆) :delta 13.20-11.87(1H,br), 8.32-8.18(1H,m), 8.05-7.85(7H,m), 7.47-7.37(2H,m), 3.88-3.76(1H,m), 1.20(3H,d,J=7.0Hz).

[0175]Example 2(5) N-[4-(1-methylbenzimidazol 2-yl) phenyl slufonyl]-D-alanine [Formula 29]

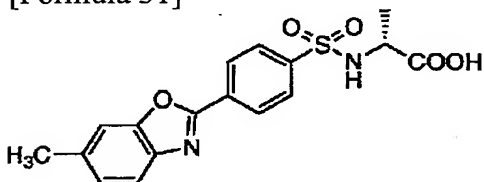


[0176]TLC:Rf 0.41 (methanol: chloroform : acetic acid : water =50:10:1:1);
NMR. (DMSO-d₆) :. delta 8.43(1H,d,J=8.2Hz), 8.10(2H,d,J=8.6Hz), 8.03(2H,d,J=8.6Hz), 7.83(2H,m), 7.50(2H,m), 3.98(3H,s), 3.89 (1H, m), 1.11 (3H, d, J= 7.3 Hz).

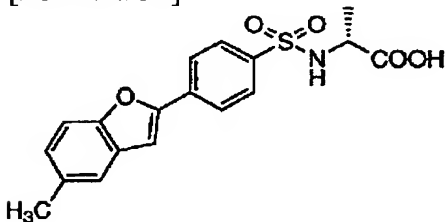
[0177]Example 2(6) N-[4-(5-methylbenzoxazol- 2-yl) phenyl slufonyl]-D-alanine [Formula 30]



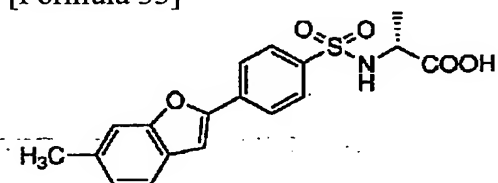
[0178]TLC:Rf 0.43 (methanol: chloroform : acetic acid : water =50:10:1:1);
 NMR. (DMSO- d_6) : δ 12.78(1H,brs), 8.38(1H,d,J=8.6Hz), 8.33(2H,d,J=8.8Hz),
 7.97(2H,d,J=8.8Hz), 7.68(1H,d,J=8.3Hz), 7.63 (1H, d, J= 1.2 Hz), 7.27 (1H, dd, J=
 1.2, 8.3 Hz), 3.85 (1H, dq, J= 8.6, 7.3 Hz), 2.45 (3H, s), 1.19 (3H,d,J=7.3Hz).
 [0179]Example 2(7) N-[4-(6-methylbenzooxazol- 2-yl) phenyl slufonyl]-D-alanine
 [Formula 31]



[0180]TLC:Rf 0.43 (methanol: chloroform : acetic acid : water =50:10:1:1);
 NMR. (DMSO- d_6) : δ 12.76(1H,brs), 8.38(1H,d,J=8.8Hz), 8.31(2H,d,J=8.6Hz),
 7.98(2H,d,J=8.6Hz), 7.72(1H,d,J=8.1Hz), 7.64 (1H, s), 7.23 (1H,d,J=8.1Hz), 3.83 (1H,
 m), 2.48 (3H, s), 7.32 (3H,d,J=7.3Hz).
 [0181]Example 2(8) N-[4-(5-methylbenzofuran-2-yl) phenyl slufonyl]-D-alanine
 [Formula 32]

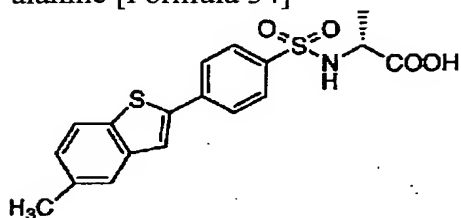


[0182]TLC:Rf 0.53 (chloroform: methanol : acetic acid =100:10:1);
 NMR. (DMSO- d_6) : δ 8.23(1H,br.d,J=8.4Hz), 8.07(2H,d,J=8.4Hz),
 7.87(2H,d,J=8.4Hz), 7.56(1H,s), 7.53(1H,d,J=8.4Hz), 7.48 (1H, br.s), 7.18
 (1H,d,J=8.4), 3.89-3.74 (1H, m), 2.40 (3H, s), 1.17 (3H,d,J=6.8Hz).
 [0183]Example 2(9) N-[4-(6-methylbenzofuran-2-yl) phenyl slufonyl]-D-alanine
 [Formula 33]



[0184]TLC:Rf 0.40 (chloroform: methanol : acetic acid =100:10:1);
 NMR. (DMSO- d_6) : δ 8.30-8.16(1H,m), 8.05(2H,d,J=8.4Hz), 7.86(2H,d,J=8.4Hz),
 7.57(1H,br.s), 7.57(1H,d,J=8.0Hz), 7.47(1H,br.s), 7.12 (1H, br.d, J= 8.0 Hz), 3.89-3.71
 (1H, m), 2.44 (3H, s), 1.17 (3H,d,J=7.2Hz).
 [0185]Example 2 (10) N-[4-(5-methyl benzothiophene 2-yl) phenyl slufonyl]-D-

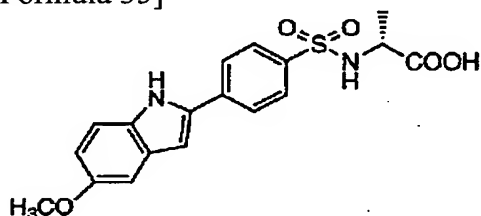
alanine [Formula 34]



[0186]TLC:Rf 0.38 (chloroform: methanol : acetic acid =100:10:1);

NMR. (DMSO- d_6) : δ 8.23(1H,br.d,J=8.4Hz), 7.96(1H,br.s), 7.95(2H,d,J=8.8Hz), 7.88(1H,d,J=8.8Hz), 7.84(2H,d,J=8.8Hz), 7.68 (1H, br.s), 7.23 (1H, dd, J= 8.2, 1.4 Hz), 3.88-3.73 (1H, m), 2.42 (3H, s), 1.18 (3H,d,J=7.0Hz).

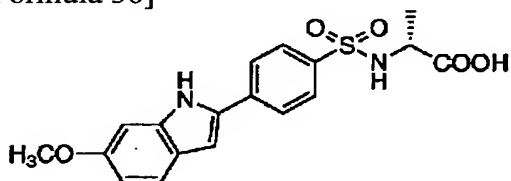
[0187]Example 2 (11) N-[4-(5-methoxy indole- 2-yl) phenyl slufonyl]-D-alanine
[Formula 35]



[0188]TLC:Rf 0.34 (methanol: chloroform : acetic acid : water =50:10:1:1);

NMR. (CD₃OD) : δ 7.91(2H,d,J=8.1Hz), 7.87(2H,d,J=8.1Hz), 7.18(1H,d,J=8.8Hz), 7.09(1H,d,J=2.6Hz), 6.80(1H,dd,J=2.6,8.8Hz, 3.92 (1H,q,J=7.3Hz), 3.81 (3H, s), 1.32 (3H, d).

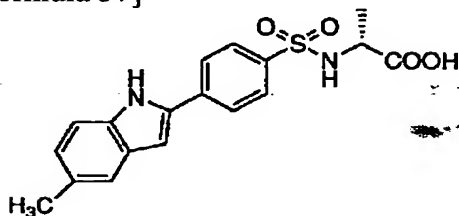
[0189]Example 2 (12) N-[4-(6-methoxy indole- 2-yl) phenyl slufonyl]-D-alanine
[Formula 36]



[0190]TLC:Rf 0.34 (methanol: chloroform : acetic acid : water =50:10:1:1);

NMR. (CD₃OD) : δ 7.75(4H,s), 7.41(1H,d,J=8.8Hz), 6.92(1H,d,J=2.4Hz), 6.88(1H,d,J<1Hz), 6.69(1H,dd,J=2.4,8.8Hz), 3.92 (1H, q, J= 7.3 Hz), 3.83 (3H, s), 1.31 (3H, d, J= 7.3 Hz).

[0191]Example 2 (13) N-[4-(5-methylindole 2-yl) phenyl slufonyl]-D-alanine
[Formula 37]



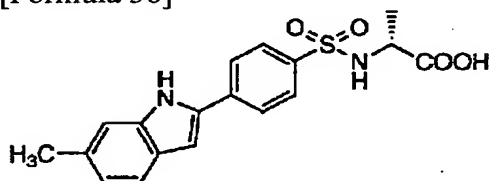
[0192]TLC:Rf 0.32 (methanol: chloroform : acetic acid : water =50:10:1:1);

NMR. (CD₃OD) : δ 7.89(2H,d,J=8.8Hz), 7.85(2H,d,J=8.8Hz), 7.32(1H,d,J=1.4Hz),

7.27(1H,d,J=8.3Hz), 6.97(1H,d,J=1.4,8.3Hz, 6.87 (1H,d,J<1Hz), 3.97 (1H,q,J=7.3Hz), 2.39 (3H, s), 1.32 (3H,d,J=7.3Hz).

[0193] Example 2 (14) N-[4-(6-methylindole 2-yl) phenyl sulfonyl]-D-alanine

[Formula 38]

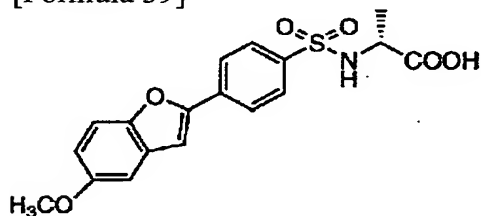


[0194] TLC:Rf 0.32 (methanol: chloroform : acetic acid : water =50:10:1:1);

NMR. (CD₃OD) : delta 7.89(2H,d,J=8.8Hz), 7.85(2H,d,J=8.8Hz), 7.42(1H,d,J=8.1Hz), 7.20(1H,d,J=1.2Hz), 6.90(1H,s), 6.89(1H, dd, J= 1.2, 8.1 Hz), 3.92 (1H,q,J=7.1Hz), 2.42 (3H, s), 1.32 (3H,d,J=7.1Hz).

[0195] Example 2 (15) N-[4-(5-methoxy benzofuran-2-yl) phenyl sulfonyl]-D-alanine

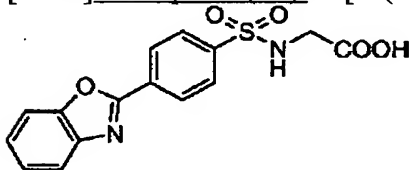
[Formula 39]



[0196] TLC:Rf 0.48 (methanol: chloroform : acetic acid : water =50:10:1:1);

NMR. (CD₃OD) : delta 7.98(2H,d,J=8.8Hz), 7.90(2H,d,J=8.8Hz), 7.41(1H,d,J=9.0Hz), 7.28(1H,s), 7.11(1H,d,J=2.4Hz), 6.91(1H, dd, J= 2.4, 9.0 Hz), 3.94 (1H,q,J=7.3Hz), 3.83 (3H, s), 1.32 (3H,d,J=7.3Hz).

[0197] Example 2 (16) N-[4-(2-benzoxazolyl) phenyl sulfonyl] glycine [Formula 40]

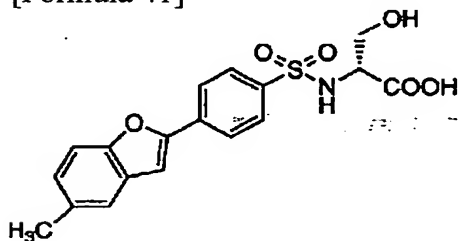


[0198] TLC:Rf 0.30 (chloroform: methanol : acetic acid =85:15:1);

NMR. (DMSO-d₆) : delta 8.38(2H,d,J=8.8Hz), 8.30(1H,t,J=6.2Hz), 8.02(2H,d,J=8.8Hz), 7.92-7.80(2H,m), 7.52-7.43(2H,m), 3.67(2H, d, J= 6.2 Hz).

[0199] Example 2 (17) N-[4-(5-methyl-benzofuran-2-yl) phenyl sulfonyl]-D-serine

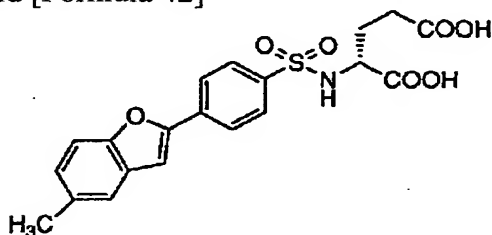
[Formula 41]



[0200] TLC:Rf 0.25 (chloroform: methanol : acetic acid =10:1:1);

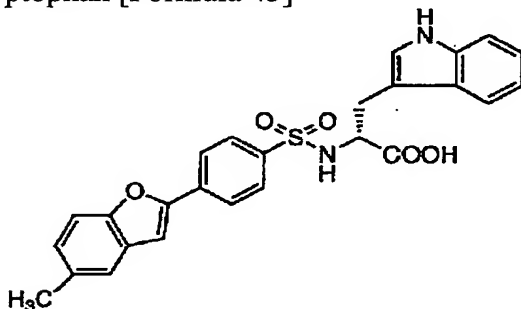
NMR(DMSO-d₆): delta 8.12(1H,d,J=8.8Hz), 8.06(2H,d,J=8.8Hz), 7.88(2H,d,8.8Hz), 7.56(1H,s), 7.53(1H,d,J=8.6Hz), 7.48(1H,br .s), 7.18(1H,d,J=8.6,1.4Hz), 5.20-

4.80(1H,br.), 3.81(1H,dt,J=8.8,5.2Hz), 3.52(2H,br.,J=5.2Hz), 2.40 (3H, s).
 [0201]Example 2 (18) N-[4-(5-methyl-benzofuran-2-yl) phenyl sulfonyl]-D-glutamic acid [Formula 42]



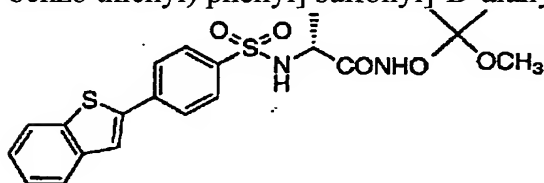
[0202]TLC:Rf 0.46 (chloroform: methanol : acetic acid =10:1:1);
 NMR(DMSO-d₆): delta 12.80(2H,br.), 8.40-8.10(1H,br.), 8.06(2H,d,J=8.8Hz),
 7.84(2H,d,J=8.8Hz), 7.55(1H,s), 7.53(1H,d,J=8.2Hz), 7.48(1H,br.s),
 7.18(1H,dd,J=8.2Hz), 3.88-3.76(1H,m), 2.40(3H,s), 2.22(2H,t,J=7.0Hz),1.95-1.57
 (2H, m).

[0203]Example 2 (19) N-[4-(5-methyl-benzofuran-2-yl) phenyl sulfonyl]-D-tryptophan [Formula 43]



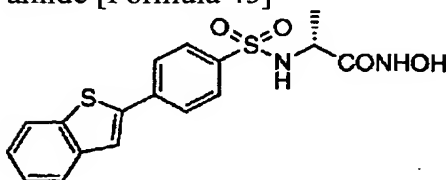
[0204]TLC:Rf 0.58 (chloroform: methanol : acetic acid =10:1:1);
 NMR(DMSO-d₆): delta 10.78(1H,br.s), 7.85(2H,d,J=8.6Hz), 7.63(2H,d,J=8.6Hz),
 7.54(1H,d,J=8.8Hz), 7.49(2H,br.s), 7.33-7.29 (1H,m), 7.22-7.15(2H,m),
 7.07(1H,d,J=2.2Hz), 6.98-6.84(2H,m), 3.96-3.88(1H,m), 3.11-2.80(2H,m), 2.41 (3H,
 s).

[0205]reference example 3N-(1-methoxy-1,1-dimethylmethoxy)- N-[N'-[[4-(2-benzo thienyl) phenyl] sulfonyl]-D-alanyl] amide [Formula 44]



[0206]In the DMF (1 ml) solution of N-(1-methoxy-1,1-dimethylmethoxy) amine (124 mg). An N-[4-(2-benzo thienyl) phenyl sulfonyl]-D-alanine (it manufactured in Example 2 (4).) (100 mg), HOBt-H₂O (42 mg), EDC-HCl (53 mg), and triethylamine (39microl) were added under ice-cooling, and were agitated under the room temperature for 14 hours. Water was added after ending reaction and ethyl acetate extracted. The saturation salt solution washed the extract and it condensed after desiccation with anhydrous sodium sulfate. Ether washed the obtained crystal and the title compound (70 mg) which has the following property value was obtained. TLC:Rf 0.17 (n-hexane: ethyl acetate =2:1).

[0207]Example 3 N-hydroxy-N-[N'-[[4-(2-benzo thienyl) phenyl] Sulfonyl]-D-alanyl] amide [Formula 45]

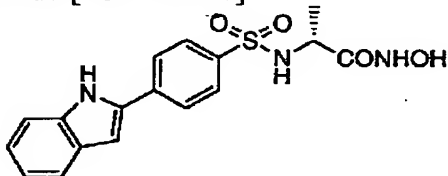


[0208]N-(1-methoxy-1,1-dimethylmethoxy)- in the dioxane (3 ml) solution of N-[N'-[[4-(2-benzo thienyl) phenyl] sulfonyl]-D-alanyl] amide (it manufactured by the reference example 3.) (65 mg). 4N chloride-dioxane (0.2 ml) was added and it agitated for 30 minutes at the room temperature. Ether washed the crystal obtained by condensing after ending reaction, and the title compound (35 mg) which has the following property value was obtained.

TLC:Rf 0.46 (chloroform: methanol : acetic acid =10:1:1);

NMR. (DMSO-d₆) : delta 10.59(1H,br.s), 8.84(1H,br.s), 8.14(1H,br.d,J=8.2Hz), 8.05-7.84(7H,m), 7.46-7.36(2H,m), 3.68-3.61(1H, m, 1.05 (3H, d, J= 7.4 Hz).

[0209]Example 3(1) N-hydroxy-N-[N'-[[4-(2-indolyl) phenyl]sulfonyl]-D-alanyl] amide [Formula 46]



[0210]The title compound which operates it like the method shown in reference example 3 -> example 3 using an N-[4-(2-indolyl) phenyl slufonyl]-D-alanine (it manufactured in Example 2.), and has the following property value was obtained.

[0211]TLC:Rf 0.14 (methanol: chloroform : acetic acid : water =100:10:1:1);

NMR(CD₃OD): delta 7.95 (2H, d, J= 8.8 Hz), 7.89 (2H, d, J= 8.8 Hz), 7.56 (1H, d, J= 7.7 Hz), 7.40 (1H, m), 7.14 (1H, m), 7.05 (1H, m), 6.98 (1H,d,J=2Hz), 3.77 (1H,q,J=7.0Hz), 1.21 (3H,d,J=7.0Hz).

[0212]

[Example(s) of Production]

It tableted, after mixing each one or less example [of pharmaceutical preparation] ingredient with a conventional method, and 100 doses of tablets which contain a 50-mg active ingredient in 1 dose were obtained.

- N-[4-(2-benzo thienyl) phenyl slufonyl]-D-alanine 5.0 g and carboxymethyl-cellulose calcium (disintegrator) 0.2 g and magnesium stearate (lubricant) 0.1 g and microcrystalline cellulose ---- 4.7 g[0213]After mixing each two or less example [of pharmaceutical preparation] ingredient with a conventional method, the solution

was sterilized with the conventional method, and it filled up the ampul with 5 ml at a time, and freeze-dried with the conventional method, and 100 ampuls which contain a 20-mg active ingredient among 1 ampul were obtained.

- N-[4-(2-benzo thienyl) phenyl slufonyl]-D-alanine 2.0 g and mannitol 20g and distilled water 500 ml

[Translation done.]

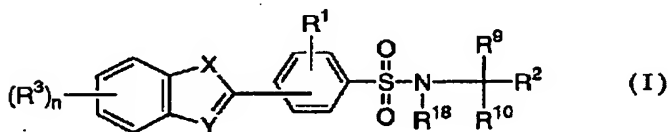
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1. This document has been translated by computer. So the translation may not reflect the original precisely.
2. **** shows the word which can not be translated.
3. In the drawings, any words are not translated.

TECHNICAL FIELD

[Field of the Invention] This invention relates to a phenyl sulfonamide derivative, its manufacturing method, and the drugs that contain the derivative as an active principle.
[0002] It is general formula (I) in more detail.
[Formula 2]



(all the signs express the same meaning as a postscript among a formula.) -- it is related with the phenyl sulfonamide derivatives shown, those nontoxic salts, those manufacturing methods, and the drugs containing them.

[Translation done.]

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PRIOR ART

[The background and conventional technology of an invention] Matrix metalaw-proteinase (it is hereafter written as MMP.) to an active center Zinc. (it is hereafter written as Zn^{2+} .) -- it being the neutral metalaw proteinase which it has, and, It is acting on growth, organization reconstruction, etc. of a joint organization, an osseous tissue, connective tissue, etc. by decomposing collagen, a laminin, proteoglycan, fibronectin, elastin, gelatin, etc. under a physiological situation. Ten or more kinds of molecular species in which MMP will differ in the primary structure by the present

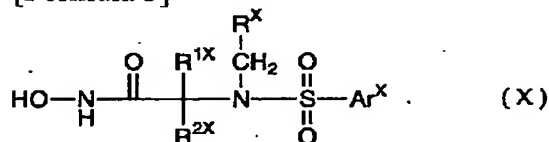
are identified. Specifically Interstitial collagenase (MMP-1), leucocyte collagenase (MMP-8), The gelatinase A (MMP-2), the gelatinase B (MMP-9), the SUTOROMU lysin 1 (MMP-3), the SUTOROMU lysin 2 (MMP-10), Mathot Rira Isin (MMP-7), etc. are mentioned.

[0004]As character common to these each enzyme, it has Zn^{2+} in (1) active center, and calcium (Ca^{2+}) is needed for enzyme activity, (2) It has [it being secreted as a latent type enzyme and receiving activation out of a cell,] high homology in (3) amino acid sequences, (4) having various extracellular matrix component resolution which exists in the living body, and (5) -- it is known that activity will be checked by organization metalaw proteinases inhibitor (TIMP) which is common inhibitor etc.

[0005]It is thought that inhibitor of MMP is useful for the prevention and/or the therapy of various diseases which are produced when secretion and activity of MMP carry out a gastric upset. For example, rheumatism, osteoarthritis, morbid osteoclasts, osteoporosis, periodontitis, interstitial nephritis, The disease of arteriosclerosis, vesicular emphysema, liver cirrhosis, cornea damage, transition permeation of a cancer cell, or growth, an autoimmune disease, the diseases (Crohn's disease, a SHUGUREN disease, etc.) by the blood vessel transmigration of the cell of a leucocyte system or permeation, the vascularization, etc. are mentioned.

[0006]Some compounds which have matrix metalaw proteinase inhibitory action are known. Especially, it is known that the substrate near the cutting point of collagen (Gly-Ile-Ala-Gly or Gly-Leu-Ala-Gly) has collagenase and high compatibility. The substrate analog matrix metalloproteinase inhibitor which has a zinc compatibility group in the cleavage site of this substrate and which performed chemical modification, Curr., [Inhibitors of matrix metalloproteinases (MMP's), Nigel RA Beeley, Phillip RJ Ansell, Andrew JP Docherty et al. currently studied. [many] Opin. Ther. Patents, 4,7-16 (1994) and Current Drugs Ltd ISSN 0962-2594 Reference]. However, since these substrate analog inhibitor is peptide analogs, it is expected that there are various problems. For this reason, to form these inhibitor into un-peptide is desired, and some are reported.

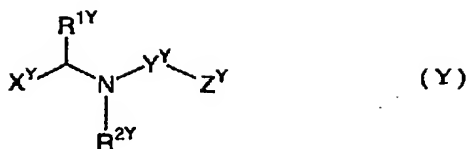
[0007]For example, in the specification of EP No. 606046, it is general formula (X). [Formula 3]



the inside of a formula, and (a) Ar^{X} -- carbocyclic or heterocyclic aryl group; R^{X} -- a hydrogen atom. ; $\text{R}^{1\text{X}}$, such as a low-grade alkyl group and carbocyclic aryl low-grade alkyl group, a hydrogen atom, Are a hydrogen atom or a low-grade alkyl group, or; or (b) R^{X} , and $\text{R}^{1\text{X}}$ become together with the chain with which they are added, and; $\text{R}^{2\text{X}}$, such as a low-grade alkyl group and carbocyclic aryl low-grade alkyl group, a 1,2,3,4-tetrahydro isoquinoline, a piperidine ring etc. -- formation; -- Ar^{X} and $\text{R}^{2\text{X}}$ having the meaning which (a) defined, or; or (c) $\text{R}^{1\text{X}}$, and $\text{R}^{2\text{X}}$ becoming together with the carbon atom in which they are added, and them, Three to C7 cycloalkane replaced by un-replacing or a low-grade alkyl group, ;, such as oxa cyclohexane and ****-cyclohexane, Ar^{X} , and $\text{R}^{2\text{X}}$ have the meaning which (a) defined. It is indicated that the aryl sulfonamide derivative shown has matrix metalaw proteinase inhibitory action.

[0008]In the specification of WO No. 9535276, it is a general formula (Y).

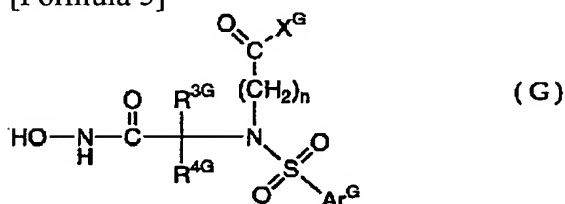
[Formula 4]



alpha-amino-acid side chain; R^{2Y} of nature [Y / the inside of a formula, and / X / 1Y / COOH group and CONHOH basis; R], or non-nature -- $Z^{1Y}Q^YW^Y$ group; Z^{1Y} -- a hydrogen atom. Aryl group etc.; (i) Q^YW^Y becomes together and A single bond, O atom, S atom, and W^YQ^Y (ii) C1 - 20 alkyl groups, etc., A single bond and W^YQ^Y (iii) C9 - 20 alkyl groups, etc., Q^Y (iv) A single bond, W^Y -- C1 - 8 alkyl-group; -- Y^Y -- SO_2 group; -- Z^Y expresses the aryl group or heteroaryl group which may be replaced arbitrarily. It is indicated that the compound shown has matrix metalaw proteinase inhibitory action.

[0009]the specification of WO No. 9627583 -- general formula (G)

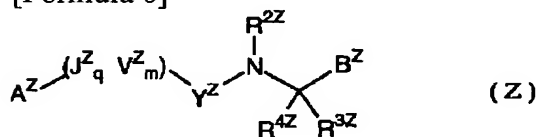
[Formula 5]



the inside of a formula, and n -- 1 - 6; X^G -- a hydroxyl group and C -- one to 6 alkoxy group, $NR^{1G}R^{2G}$; R^{3G} and R^{4G} A hydrogen atom, C1 - 6 alkyl groups, etc. : Ar^G An aryl group (C6-10), (C5-9) A heteroaryl group, an alkyl (C1-6) (C6-10) aryl group, (C1-6) An alkoxy (C6-10) aryl group, a $_2$ (alkoxy (C1-6)) (C6-10) aryl group, (C6-10) An aryloxy (C6-10) aryl group, a heteroaryloxy (C5-9) (C6-10) aryl group, (C1-6) An alkyl (C5-9) heteroaryl group, an alkoxy (C1-6) (C5-9) heteroaryl group, (C1-6) A $_2$ (C5-9) heteroaryl group (alkoxy), (C6-10) An aryloxy (C5-9) heteroaryl group and a heteroaryloxy (C5-9) (C5-9) heteroaryl group are expressed. It is indicated that the compound shown has matrix metalaw proteinase inhibitory action.

[0010]On the other hand, in the specification of WO No. 9315047, it is a general formula (Z).

[Formula 6]

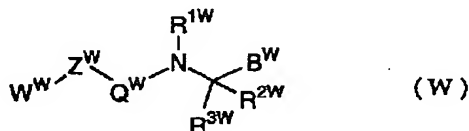


(-- the inside of a formula, and A^Z -- a) -- a $-Q^Z-X^Z$ group (Q^Z-O-) S-, a $-NR^Z$ -basis, a single bond, and X^Z -The aromatic ring or heterocycle of 5 and 6 members, A b)-CN basis, a $-NO_2$ group, a $-N_3$ group, a $-NR^ZR^{1Z}$ group, - OR^Z group, a $-COR^Z$ group, a $-CO_2R^Z$ group (independently R^Z and R^{1Z} , respectively); J^Z , such as a hydrogen atom, C1 - 18 alkyl groups, C2 - 18 alkenyl groups, the alkanediyl group of C1 - 8 of bivalence, An alkenediyl group or an alkynediyl group; V^Z A phenylene group, 0 or 1; Y^Z ; q , such as a francdiyl group, a thiophenediyl group, and a thiazolediyl group, and m A single bond, - A CH_2 -basis, a $-C(=O)$ -basis, a $-C(=S)$ -basis, a $-S(=O)_2$ -basis, or a $-P(=O)$ (one to OC6 alkyl)-basis (however, when Y^Z is a $-S(=O)_2$ -basis) Q^Z does not express a single bond.; R^{2Z} A hydrogen atom, C1 - 6 alkyl groups, C2 - 6 alkenyl

groups, C2 - 6 alkynyl groups, $-R^{3Z}$, such as CO (one to C6 alkyl) basis and a $-CO_2$ (one to C6 alkyl) basis, and R^{4Z} , respectively independently, B^Z , such as a hydrogen atom, a halogen atom, C1 - 6 alkyl groups, and a natural amino acid side chain, -- an aZ^ZR^{8Z} group (Z^Z -- a single bond.) $-C(=O)$ -basis, a $-C(=O)$ O-basis, a $-CH_2O$ -basis, etc., R^{8Z} A hydrogen atom, C1 - 18 alkyl groups, C2 - 18 alkenyl groups, A b[, such as C2 - 18 alkynyl groups,]- $CH_2NR^{9Z}R^{10Z}$ group or a $-CONR^{9Z}R^{10Z}$ group (independently R^{9Z} and R^{10Z} , respectively) A hydrogen atom, C1 - 18 alkyl groups, C2 - 18 alkenyl groups, C2 - 18 alkynyl groups, etc., c) E^Z group (5, 6 member heterocycle which contain the hetero atom in which E^Z is chosen from a nitrogen atom, an oxygen atom, and a sulfur atom one or more), Or a d- CH_2E^Z group, a $-C(=O)NHE^Z$ group, or a $-C(=O)NHCH_2-E^Z$ group is expressed. It is indicated that the compound shown is useful as a PAF antagonist.

[0011] In the Patent Publication Heisei No. (WO-9314072) 502742 [seven to] specification, it is a general formula (W).

[Formula 7]



(Among a formula, W^W was arbitrarily replaced by one or more C1 - 6 alkyl-group substituents, and) Pyrid 3-yl groups, benzimidazole 1-yl groups, 4,5-imidazo[c] pyridine- 1-yl groups, 4,5-imidazo[c] pyridine- 3-yl groups and 4,5-imidazo[c] pyridine- 5-yl groups; Z^W The divalent alkanediyl group of aC2-12, An alkenediyl group, an alkynediyl group, etc. to b arbitration A hydroxyl group, -O (C1-6) alkyl group, the $-(CH_2)_qU^W(CH_2)_r$ -basis (q -- 0 - 3; U^W -- benzenediyl.) replaced by one or more bases chosen from the halogen atom and the nitrile group -O-, -S-, a francdiyl group, a thiophenediyl group, etc. -- etc. --; Q^W -- a carbonyl group. Thiocarbonyl group, sulfonyl group, or single bond; R^{1W} A hydrogen atom, R^{2W} , such as C1 - 6 alkyl groups, C2 - 6 alkenyl groups, etc. which were replaced by one or more bases arbitrarily chosen from C1 - 6 alkyl groups, -O (C1-6) alkyl group, the halogen atom, the $-CF_3$ group, and CN basis, a hydrogen atom, a halogen atom, C1 - 6 alkyl groups, C2 - 6 alkenyl groups which were arbitrarily replaced with one or more halogen atoms, ;, such as a side chain of natural amino acid, -- R^{3W} -- hydrogen atom and halogen atom; B^W -- an $a-V^WR^{8W}$ group (V^W -- a $-C(=O)$ -basis.) ; R^{8W} , such as a $C(=O)O$ -basis and a $-CH_2O$ -basis, -A hydrogen atom, A b[, such as C1 - 18 alkyl groups, C2 - 6 alkenyl groups,]- $CH_2NR^{9W}R^{10W}$ group, a $-CONR^{9W}R^{10W}$ group, etc. are expressed. It is indicated that the compound shown is useful as a PAF antagonist.

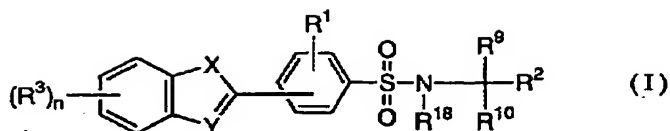
[0012]

[Objects of the Invention] Matrix [this invention persons] metalaw proteinase, for example, gelatinase, As a result of inquiring wholeheartedly in order to find out the compound which has inhibitory action to SUTOROMU lysin or collagenase, the new phenyl sulfonamide derivative shown by general formula (I) found out attaining the purpose.

[0013]

[Description of the Invention] This invention is 1 general-formula (I).

[Formula 8]



(R¹ among a formula a hydrogen atom, or C1 - 4 alkyl groups) [express and] R² expresses a -COOR⁴ group or a -CONHOR⁵ group, R⁴ (1) hydrogen atom, (2) C1 - 8 alkyl group, and (3) phenyl group, Or (4) phenyl groups, a -OCOR⁶ group (R⁶ expresses C1 - 4 alkyl groups among a basis.), or a -CONR⁷R⁸ group (independently R⁷ and R⁸ among a basis, respectively) A hydrogen atom, or C1 - 4 alkyl groups is expressed. C1 replaced by either - 4 alkyl groups are expressed, [0014]R⁵ expresses C1 replaced by the hydrogen atom, C1 - 8 alkyl groups, the phenyl group, or the phenyl group - 4 alkyl groups, X is an oxygen atom, a sulfur atom, or a -NR¹⁷ group (R¹⁷ among a basis). A hydrogen atom, C1 - 4 alkyl groups, C1 replaced by the phenyl group - 4 alkyl groups, C1 replaced by C1 - 8 alkoxy carbonyl groups, or a phenyl group - 4 alkoxy carbonyl groups are expressed. It expresses, Y expresses CH basis or a nitrogen atom, and R³ A hydrogen atom, C1 - 4 alkyl groups, C1 - 4 alkoxy groups, a halogen atom, a trifluoromethyl group, a hydroxyl group, A carboxyl group, C1 - 8 alkoxy carbonyl groups, a nitro group, a -NR⁷R⁸ group (among a basis) R⁷ and R⁸ express the same meaning as the above. Or a -CONR⁷R⁸ group (R⁷ and R⁸ express the same meaning as the above among a basis.) is expressed, and n expresses the integer of 1-4, [0015]Independently R⁹ and R¹⁰, respectively (1) hydrogen atom, (2) C1 - 8 alkyl groups (however, one -CH₂-basis in an alkyl group may be changed with one sulfur atom.), a (3)-COR¹¹ group (the inside of a basis, and R¹¹ -- a hydroxyl group and C -- one to 8 alkyl group) C1 - 4 alkoxy groups, or the -NR¹⁵R¹⁶ group (independently R¹⁵ and R¹⁶ among a basis, respectively) replaced by C1 - 8 alkoxy groups, the phenoxy group, and the phenyl group C1 replaced by the hydrogen atom, C1 - 4 alkyl groups, the phenyl group, one piece, or two phenyl groups - 4 alkyl groups are expressed. It expresses. (4) a ring group and (5) heterocycle groups (the ring of the above (4) or the heterocycle of the above (5) may be replaced by one to three C1 - 4 alkyl groups, C1 - 4 alkoxy groups, the halogen atom, the hydroxyl group, and the trifluoromethyl group.) -- or [0016](6) C1 replaced by one basis chosen from the following (i) - (viii) - 8 alkyl groups, (i) A -COR¹¹ group (R¹¹ expresses the same meaning as the above among a basis.), (ii) C1 - 4 alkoxy groups, a (iii) hydroxyl group, a (iv) benzyloxy group, (v) A guanidino group, a (vi) -NR¹²R¹³ group (independently R¹² and R¹³ among a basis, respectively) A hydrogen atom, C1 - 4 alkyl groups, or a COOR¹⁴ group (among a basis) R¹⁴ expresses C1 - 4 alkyl groups, or benzyl. It expresses. (vii) Express a ring group or a (viii) heterocycle group (the ring of said (vii) or the heterocycle of said (viii) may be replaced by one to three C1 - 4 alkyl groups, C1 - 4 alkoxy groups, the halogen atom, the hydroxyl group, and the trifluoromethyl group.), [0017]C1 by which R¹⁸ was replaced by the hydrogen atom, C1 - 4 alkyl groups, and the phenyl group - 4 alkyl groups, C1 replaced by C1 - 8 alkoxy carbonyl groups, or a phenyl group - 4 alkoxy carbonyl groups are expressed. The phenyl sulfonamide derivatives shown or those nontoxic salts, [0018]2) It is related with the drugs which contain the manufacturing method of the phenyl sulfonamide derivatives shown by general formula (I), and those nontoxic salts, the phenyl sulfonamide derivatives shown by 3 general-formula (I), and those nontoxic salts as an active principle.

[0019]Especially in this invention, it points, and as long as there is nothing, an isomer

includes this all. For example, a thing of a straight chain and a thing of a branched chain are contained in an alkyl group, an alkoxy group, and an alkylene group. A double bond in an alkenylene group contains what is E, Z, and EZ mixture. An isomer produced by existence of asymmetric carbon atoms in case an alkyl group, an ARUKOSHIKI group, and an alkylene group of a branched chain exist is also contained.

[0020]The inside of general formula (I), $R^1, R^3, R^6, R^7, R^8, R^{12}, R^{13}, R^{14}$, C1 - 4 alkyl groups, or R^4 expressed by R^{15}, R^{16}, R^{17} , and R^{18} , C1 - 4 alkyl groups (a substituent of a ring group or a heterocycle group is also included.) in $R^5, R^9, R^{10}, R^{15}, R^{16}, R^{17}$, and R^{18} are methyl, ethyl, propyl, butyl groups, and these isomers. The inside of general formula (I), R^4, R^5, R^9, R^{10} , C1 - 8 alkyl groups in C1 expressed by $R^{11} - 8$ alkyl groups or R^9 , and R^{10} are methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl groups, and these isomers. One $-CH_2-$ basis expressed by R^9 and R^{10} among general formula (I) with C1 replaced with one sulfur atom - 8 alkyl groups. Methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, an octyl group, and one $-CH_2-$ basis in these isomer groups express a basis changed with one sulfur atom. For example, a $-SH$, $-CH_2-SH$, and $-CH_2CH_2-S-CH_3$ group is mentioned.

[0021]C1 - 4 alkoxy groups, or R^9 expressed by R^3 among general formula (I), C1 - 4 alkoxy groups (the substituent of a ring group or a heterocycle group is also included.) in R^{10} and R^{11} are methoxy and ethoxy ** propoxy, butoxy groups, and these isomers. C1 expressed by $R^{11} - 8$ alkoxy groups are methoxy and ethoxy ** propoxy, butoxy, pentyloxy one, hexyloxy one, heptyloxy, octyloxy groups, and these isomers among general formula (I).

[0022]With C1 expressed by R^3, R^{17} , and R^{18} among general formula (I) - 8 alkoxy carbonyl groups. They are carbomethoxy, ethoxycarbonyl, carbopropoxy, butoxycarbonyl, pentyloxy carbonyl, hexyloxy carbonyl, heptyloxy carbonyl, octyloxy carbonyl groups, and these isomers. C1 - 4 alkoxy carbonyl groups in R^{17} and R^{18} are carbomethoxy, ethoxycarbonyl, carbopropoxy, butoxycarbonyl groups, and these isomers among general formula (I).

[0023]The ring in R^9 and R^{10} means the with a carbon number of 15 or less of a monocycle and two rings aromatic ring in which all may be saturated in part among general formula (I). As these rings, the ring with which benzene, naphthalene, indene, an azulene, a fluorene, the phenanthrene, anthracene, an acenaphthylene, biphenylene rings and these parts, or all are saturated is mentioned, for example. The monocycle of 5 - 15 member or 2 cyclic heterocycle containing one piece or two nitrogen atoms, one oxygen atom, and/or one sulfur atom is expressed as the heterocycle in R^9 and R^{10} among general formula (I). With the monocycle of 5 - 15 member or 2 cyclic heterocycle containing one piece or two nitrogen atoms, one oxygen atom, and/or one sulfur atom. The monocycle of 5 containing one piece or two nitrogen atoms, one oxygen atom, and/or one sulfur atom - 15 members, 2 cyclic heterocyclic aryl, or its in part or all saturated thing is contained.

[0024]As the monocycle of 5 containing above mentioned one piece or two nitrogen atoms, one oxygen atom, and/or one sulfur atom - 15 members, or 2 cyclic heterocyclic aryl, Pyrrole, imidazole, a pyrazole, pyridine, pyrazine, pyrimidine, Pyridazine, azepine, diazepine, a franc, Piran, oxepin, Oxazepine, a thiophene, thiazine (thiopyran), thiepine, oxazol, An isoxazole, a thiazole, isothiazole, oxadiazole, An oxaazine, oxa diazine, oxa azepine, oxa diazepine, Thiadiazole, a thia azine, thiadiazin, thia azepine, thia diazepine, Indole, isoindole, benzofuran, isobenzofuran, benzothiophene, Isobenzothiophene, indazole, quinoline, an isoquinoline, phthalazine, NAFUCHI lysine, quinoxaline, quinazoline, cinnoline, benzooxazol, benzothiazole, a

benzimidazole ring, etc. are mentioned.

[0025] As what was in part or all saturated with a monocycle of 5 - 15 member or 2 cyclic heterocycle containing said one piece or two nitrogen atoms, one oxygen atom, and/or one sulfur atom, Pyrroline, pyrrolidine, imidazoline, imidazolidine, pyrazoline, Pyrazolidine, piperidine, a piperazine, tetrahydro pyrimidine, Tetrahydro pyridazine, dihydrofuran, a tetrahydrofuran, a dihydropyran, Tetrahydropyran, a dihydrothiophene, tetrahydrothiophene, Dihydrothiayne (dihydrothiopyran), tetrahydro thiayne (tetrahydro thiopyran), Dihydrooxazol, tetrahydro oxazol, a dihydroisoxazole, A tetrahydro isoxazole, a dihydrothiazole, a tetrahydro thiazole, Dihydroisothiazole, tetrahydro isothiazole, morpholine, Thiomorpholine, indoline, isoindoline, dihydrobenzofuran, Par hydronaliumbenzofuran, dihydroisobenzofuran, par hydronaliumisobenzofuran, dihydrobenzothiophene, par hydronalium benzothiophene, dihydroiso benzothiophene, par hydronaliumiso benzothiophene, Dihydroindazole, par hydronalium indazole, dihydroquinoline, Tetrahydroquinoline, par hydronaliumquinoline, a dihydroisoquinoline, Tetrahydroisoquinoline, a par hydronaliumisoquinoline, dihydrophthalazine, Tetrahydro phthalazine, par hydronaliumphthalazine, dihydroNAFUCHI lysine, Tetrahydro NAFUCHI lysine, par hydronalium NAFUCHI lysine, dihydroquinoxaline, Tetrahydro quinoxaline, par hydronaliumquinoxaline, dihydroquinazoline, Tetrahydro quinazoline, par hydronaliumquinazoline, dihydrocinnoline, Tetrahydro cinnoline, par hydronalium cinnoline, dihydrobenzooxazol, par hydronaliumbenzooxazol, dihydrobenzothiazole, par hydronaliumbenzothiazole, dihydrobenzimidazole, a par hydronaliumbenzimidazole ring, etc. are mentioned.

[0026] The halogen atom as the ring group in the halogen atom or R^9 expressed by R^3 , and R^{10} or a substituent of a heterocycle group means chlorine, bromine, fluoride, and iodine atoms among general formula (I). R^9 and R^{10} may express an alpha-amino-acid side chain among general formula (I). As alpha-amino acid, a glycine, an alanine, serine, threonine, Cystein, valine, methionine, leucine, isoleucine, phenylalanine, tyrosine, aspartic acid, glutamic acid, asparagine, arginine, lysine, histidine, tryptophan, glutamine, etc. are mentioned. An alpha-amino-acid derivative is contained in the alpha-amino acid, and the alpha-amino acid of D object, L object and DL mixtures, or those ARO objects is also contained in it.

[0027]

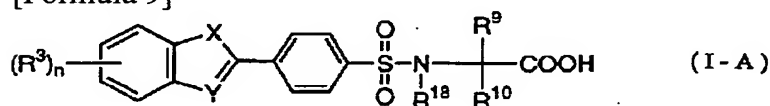
[Salt] All the nontoxic salts are included in this invention. For example, a general salt, acid addition salt, a hydrate salt, etc. are mentioned. this invention compound shown by general formula (I) is changed into a salt corresponding by a publicly known method. The water-soluble thing of a salt without toxicity is preferred. As a suitable salt, the salt of alkaline metals (potassium, sodium, etc.), The salt of alkaline-earth metals (calcium, magnesium, etc.), ammonium salt, the organic amine (tetramethylammonium and triethylamine.) permitted pharmacologically Salts, such as methylamine, dimethylamine, cyclopentyl amine, benzylamine, phenethylamine, piperidine, monoethanolamine, diethanolamine, tris(hydroxymethyl) amine, lysine, arginine, and an N-methyl-D-glucamine, are mentioned.

[0028] this invention compound shown by general formula (I) is changed into acid addition salt corresponding by a publicly known method. The water-soluble thing of acid addition salt without toxicity is preferred. As suitable acid addition salt, a hydrochloride, the hydrobromate, sulfate, an phosphate, An inorganic acid salt like a nitrate or acetate, trifluoroacetate, a lactate, A tartrate, an oxalate, fumaric acid chloride, a maleate, citrate, a benzoate, methanesulfon acid chloride, an ethane-sulfonic-acid salt, a benzenesulfonic acid salt, a toluenesulfonic acid salt, an isethionic

acid salt, a glucuronic acid salt, and organic acid salt like gluconate are mentioned. this invention compound shown by general formula (I) or its salt is also convertible for a hydrate by a publicly known method.

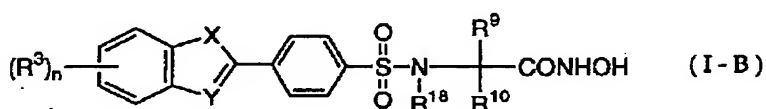
[0029] As a desirable compound among this invention compounds shown by general formula (I), it is a general formula (I-A).

[Formula 9]



(all the signs express the same meaning as the above among a formula.) -- the compound shown and general formula (I-B)

[Formula 10]

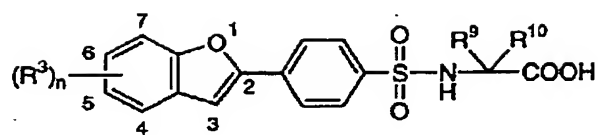


(all the signs express the same meaning as the above among a formula.) -- the compound shown is mentioned. The compound indicated from the following table 1 to Table 32, the compound indicated in those nontoxic salts and examples, etc. are mentioned more preferably. Me expresses a methyl group among front [following each].

[0030]

[Table 1]

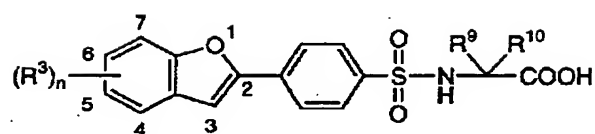
表 1



番号	$(R^3)_n$ —	R^9 R^{10}	番号	$(R^3)_n$ —	R^9 R^{10}
1	H		6	5-CH ₃	
2	H		7	5-CH ₃	
3	H		8	5-CH ₃	
4	H		9	5-CH ₃	
5	H		10	5-CH ₃	

[0031]
[Table 2]

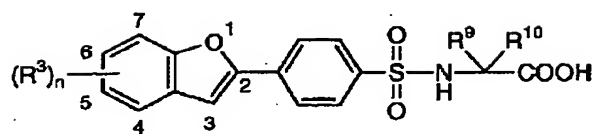
表1 (つづき)



番号	(R ³) _n —	$\begin{array}{c} \text{R}^9 \quad \text{R}^{10} \\ \diagdown \quad \diagup \\ \text{C} \end{array}$	番号	(R ³) _n —	$\begin{array}{c} \text{R}^9 \quad \text{R}^{10} \\ \diagdown \quad \diagup \\ \text{C} \end{array}$
1 1	6-CH ₃		1 6	5,6-diCH ₃	
1 2	6-CH ₃		1 7	5,6-diCH ₃	
1 3	6-CH ₃		1 8	5,6-diCH ₃	
1 4	6-CH ₃		1 9	5,6-diCH ₃	
1 5	6-CH ₃		2 0	5,6-diCH ₃	

[0032]
[Table 3]

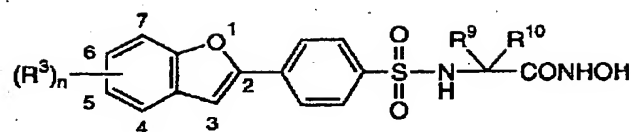
表1 (つづき)



番号	(R ³) _n —	R ⁹ R ¹⁰	番号	(R ³) _n —	R ⁹ R ¹⁰
2 1	5-OCH ₃		2 6	6-OCH ₃	
2 2	5-OCH ₃		2 7	6-OCH ₃	
2 3	5-OCH ₃		2 8	6-OCH ₃	
2 4	5-OCH ₃		2 9	6-OCH ₃	
2 5	5-OCH ₃		3 0	6-OCH ₃	

[0033]
[Table 4]

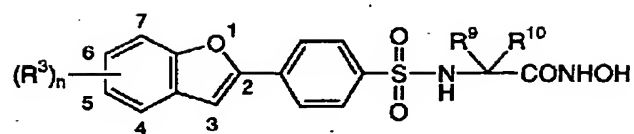
表 2



番号	$(R^3)_n$	$R^9 R^{10}$	番号	$(R^3)_n$	$R^9 R^{10}$
1	H		6	5-CH ₃	
2	H		7	5-CH ₃	
3	H		8	5-CH ₃	
4	H		9	5-CH ₃	
5	H		10	5-CH ₃	

[0034]
[Table 5]

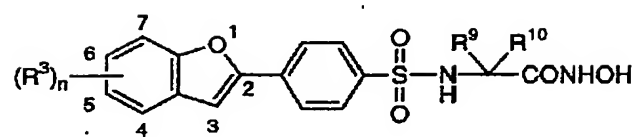
表2 (つづき)



番号	(R³) _n —	$\begin{array}{c} \text{R}^9 \quad \text{R}^{10} \\ \diagdown \quad \diagup \\ \text{C} \end{array}$	番号	(R³) _n —	$\begin{array}{c} \text{R}^9 \quad \text{R}^{10} \\ \diagdown \quad \diagup \\ \text{C} \end{array}$
1 1	6-CH ₃		1 6	5,6-diCH ₃	
1 2	6-CH ₃		1 7	5,6-diCH ₃	
1 3	6-CH ₃		1 8	5,6-diCH ₃	
1 4	6-CH ₃		1 9	5,6-diCH ₃	
1 5	6-CH ₃		2 0	5,6-diCH ₃	

[0035]
[Table 6]

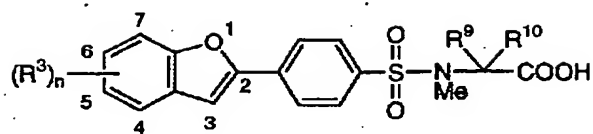
表2 (つづき)



番号	(R ³) _n —	$\begin{array}{c} \text{R}^9 \quad \text{R}^{10} \\ \diagdown \quad \diagup \\ \text{C} \end{array}$	番号	(R ³) _n —	$\begin{array}{c} \text{R}^9 \quad \text{R}^{10} \\ \diagdown \quad \diagup \\ \text{C} \end{array}$
2 1	5-OCH ₃		2 6	6-OCH ₃	
2 2	5-OCH ₃		2 7	6-OCH ₃	
2 3	5-OCH ₃		2 8	6-OCH ₃	
2 4	5-OCH ₃		2 9	6-OCH ₃	
2 5	5-OCH ₃		3 0	6-OCH ₃	

[0036]
[Table 7]

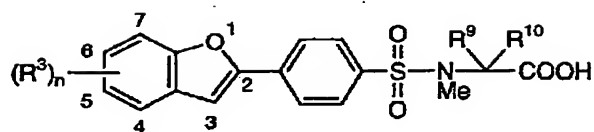
表 3



番号	(R ³) _n —	$\begin{array}{c} R^9 \\ \diagup \quad \diagdown \\ R^{10} \end{array}$	番号	(R ³) _n —	$\begin{array}{c} R^9 \\ \diagup \quad \diagdown \\ R^{10} \end{array}$
1	H		6	5-CH ₃	
2	H		7	5-CH ₃	
3	H		8	5-CH ₃	
4	H		9	5-CH ₃	
5	H		10	5-CH ₃	

[0037]
[Table 8]

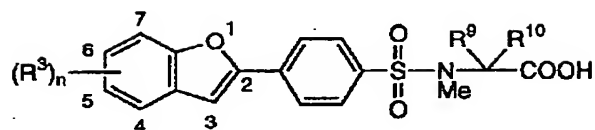
表3 (つづき)



番号	(R³) _n —	$\begin{array}{c} R^9 \\ \diagup \quad \diagdown \\ R^{10} \end{array}$	番号	(R³) _n —	$\begin{array}{c} R^9 \\ \diagup \quad \diagdown \\ R^{10} \end{array}$
1 1	6-CH ₃		1 6	5,6-diCH ₃	
1 2	6-CH ₃		1 7	5,6-diCH ₃	
1 3	6-CH ₃		1 8	5,6-diCH ₃	
1 4	6-CH ₃		1 9	5,6-diCH ₃	
1 5	6-CH ₃		2 0	5,6-diCH ₃	

[0038]
[Table 9]

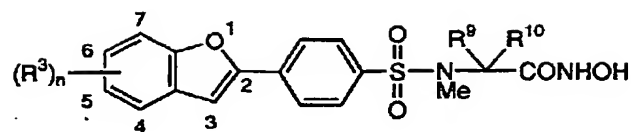
表3 (つづき)



番号	(R³) _n —	R⁹ R¹⁰	番号	(R³) _n —	R⁹ R¹⁰
2 1	5-OCH ₃		2 6	6-OCH ₃	
2 2	5-OCH ₃		2 7	6-OCH ₃	
2 3	5-OCH ₃		2 8	6-OCH ₃	
2 4	5-OCH ₃		2 9	6-OCH ₃	
2 5	5-OCH ₃		3 0	6-OCH ₃	

[0039]
[Table 10]

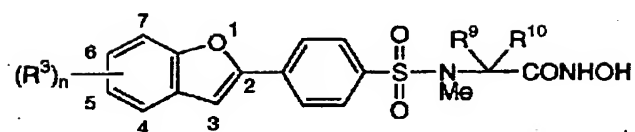
表 4



番号	(R ³) _n —	$\begin{array}{c} R^9 \\ \diagup \quad \diagdown \\ R^{10} \end{array}$	番号	(R ³) _n —	$\begin{array}{c} R^9 \\ \diagup \quad \diagdown \\ R^{10} \end{array}$
1	H		6	5-CH ₃	
2	H		7	5-CH ₃	
3	H		8	5-CH ₃	
4	H		9	5-CH ₃	
5	H		10	5-CH ₃	

[0040]
[Table 11]

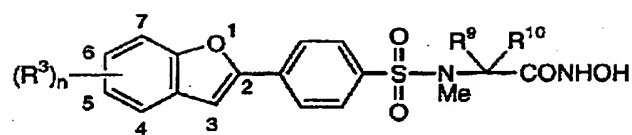
表 4 (つづき)



番号	(R ³) _n —	$\begin{array}{c} R^9 \\ \diagup \\ R^{10} \end{array}$	番号	(R ³) _n —	$\begin{array}{c} R^9 \\ \diagup \\ R^{10} \end{array}$
1 1	6-CH ₃		1 6	5,6-diCH ₃	
1 2	6-CH ₃		1 7	5,6-diCH ₃	
1 3	6-CH ₃		1 8	5,6-diCH ₃	
1 4	6-CH ₃		1 9	5,6-diCH ₃	
1 5	6-CH ₃		2 0	5,6-diCH ₃	

[0041]
[Table 12]

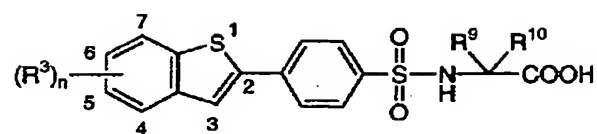
表4 (つづき)



番号	(R³) _n —	$\begin{array}{c} \text{R}^9 \quad \text{R}^{10} \\ \diagdown \quad \diagup \\ \text{C} \end{array}$	番号	(R³) _n —	$\begin{array}{c} \text{R}^9 \quad \text{R}^{10} \\ \diagdown \quad \diagup \\ \text{C} \end{array}$
2 1	5-OCH ₃		2 6	6-OCH ₃	
2 2	5-OCH ₃		2 7	6-OCH ₃	
2 3	5-OCH ₃		2 8	6-OCH ₃	
2 4	5-OCH ₃		2 9	6-OCH ₃	
2 5	5-OCH ₃		3 0	6-OCH ₃	

[0042]
[Table 13]

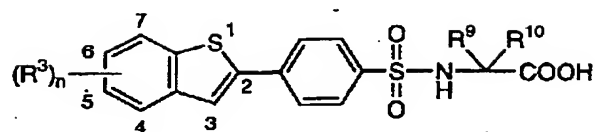
表 5



番号	(R ³) _n —	$\begin{array}{c} R^9 \\ \diagup \\ R^{10} \end{array}$	番号	(R ³) _n —	$\begin{array}{c} R^9 \\ \diagup \\ R^{10} \end{array}$
1	H		6	5-CH ₃	
2	H		7	5-CH ₃	
3	H		8	5-CH ₃	
4	H		9	5-CH ₃	
5	H		10	5-CH ₃	

[0043]
[Table 14]

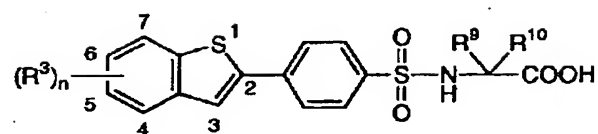
表 5 (つづき)



番号	(R ³) _n —	R ⁹ R ¹⁰	番号	(R ³) _n —	R ⁹ R ¹⁰
1 1	6-CH ₃		1 6	5,6-diCH ₃	
1 2	6-CH ₃		1 7	5,6-diCH ₃	
1 3	6-CH ₃		1 8	5,6-diCH ₃	
1 4	6-CH ₃		1 9	5,6-diCH ₃	
1 5	6-CH ₃		2 0	5,6-diCH ₃	

[0044]
[Table 15]

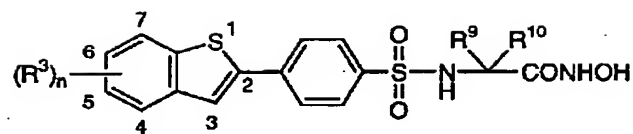
表 5 (つづき)



番号	(R ³) _n —	$\begin{array}{c} \text{R}^9 \quad \text{R}^{10} \\ \diagdown \quad \diagup \\ \text{C} \end{array}$	番号	(R ³) _n —	$\begin{array}{c} \text{R}^9 \quad \text{R}^{10} \\ \diagdown \quad \diagup \\ \text{C} \end{array}$
2 1	5-OCH ₃		2 6	6-OCH ₃	
2 2	5-OCH ₃		2 7	6-OCH ₃	
2 3	5-OCH ₃		2 8	6-OCH ₃	
2 4	5-OCH ₃		2 9	6-OCH ₃	
2 5	5-OCH ₃		3 0	6-OCH ₃	

[0045]
[Table 16]

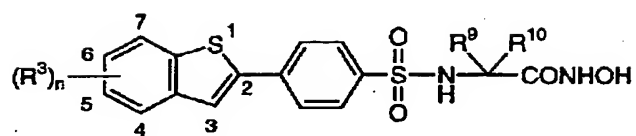
表 6



番号	(R ³) _n —	$\begin{array}{c} \text{R}^9 \quad \text{R}^{10} \\ \diagdown \quad \diagup \\ \text{C} \end{array}$	番号	(R ³) _n —	$\begin{array}{c} \text{R}^9 \quad \text{R}^{10} \\ \diagdown \quad \diagup \\ \text{C} \end{array}$
1	H		6	5-CH ₃	
2	H		7	5-CH ₃	
3	H		8	5-CH ₃	
4	H		9	5-CH ₃	
5	H		10	5-CH ₃	

[0046]
[Table 17]

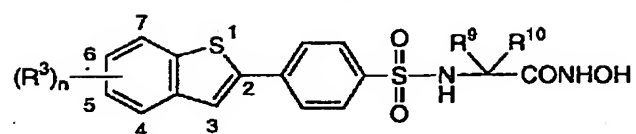
表6 (つづき)



番号	(R ³) _n —	$\begin{array}{c} R^9 \\ \diagup \quad \diagdown \\ R^{10} \end{array}$	番号	(R ³) _n —	$\begin{array}{c} R^9 \\ \diagup \quad \diagdown \\ R^{10} \end{array}$
1 1	6-CH ₃		1 6	5,6-diCH ₃	
1 2	6-CH ₃		1 7	5,6-diCH ₃	
1 3	6-CH ₃		1 8	5,6-diCH ₃	
1 4	6-CH ₃		1 9	5,6-diCH ₃	
1 5	6-CH ₃		2 0	5,6-diCH ₃	

[0047]
[Table 18]

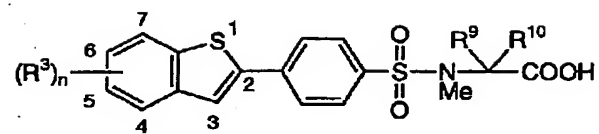
表 6 (つづき)



番号	(R ³) _n —	R ⁹ R ¹⁰	番号	(R ³) _n —	R ⁹ R ¹⁰
2 1	5-OCH ₃		2 6	6-OCH ₃	
2 2	5-OCH ₃		2 7	6-OCH ₃	
2 3	5-OCH ₃		2 8	6-OCH ₃	
2 4	5-OCH ₃		2 9	6-OCH ₃	
2 5	5-OCH ₃		3 0	6-OCH ₃	

[0048]
[Table 19]

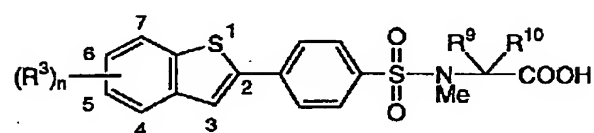
表 7



番号	(R ³) _n —	R ⁹ R ¹⁰	番号	(R ³) _n —	R ⁹ R ¹⁰
1	H		6	5-CH ₃	
2	H		7	5-CH ₃	
3	H		8	5-CH ₃	
4	H		9	5-CH ₃	
5	H		10	5-CH ₃	

[0049]
[Table 20]

表7 (つづき)

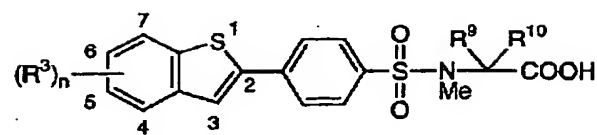


番号	(R ³) _n —	$\begin{array}{c} \text{R}^9 \quad \text{R}^{10} \\ \diagdown \quad / \\ \text{N} \end{array}$	番号	(R ³) _n —	$\begin{array}{c} \text{R}^9 \quad \text{R}^{10} \\ \diagdown \quad / \\ \text{N} \end{array}$
1 1	6-CH ₃		1 6	5,6-diCH ₃	
1 2	6-CH ₃		1 7	5,6-diCH ₃	
1 3	6-CH ₃		1 8	5,6-diCH ₃	
1 4	6-CH ₃		1 9	5,6-diCH ₃	
1 5	6-CH ₃		2 0	5,6-diCH ₃	

[0050]

[Table 21]

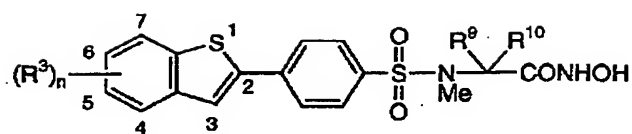
表7 (つづき)



番号	(R ³) _n —	$\begin{array}{c} \text{R}^9 \quad \text{R}^{10} \\ \diagdown \quad \diagup \\ \text{C} \end{array}$	番号	(R ³) _n —	$\begin{array}{c} \text{R}^9 \quad \text{R}^{10} \\ \diagdown \quad \diagup \\ \text{C} \end{array}$
2 1	5-OCH ₃		2 6	6-OCH ₃	
2 2	5-OCH ₃		2 7	6-OCH ₃	
2 3	5-OCH ₃		2 8	6-OCH ₃	
2 4	5-OCH ₃		2 9	6-OCH ₃	
2 5	5-OCH ₃		3 0	6-OCH ₃	

[0051]
[Table 22]

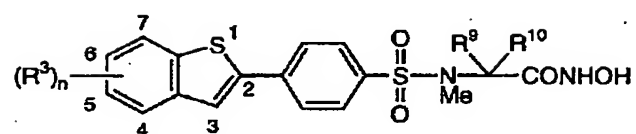
表 8



番号	(R ³) _n —	R ⁹ R ¹⁰	番号	(R ³) _n —	R ⁹ R ¹⁰
1	H		6	5-CH ₃	
2	H		7	5-CH ₃	
3	H		8	5-CH ₃	
4	H		9	5-CH ₃	
5	H		10	5-CH ₃	

[0052]
[Table 23]

表 8 (つづき)

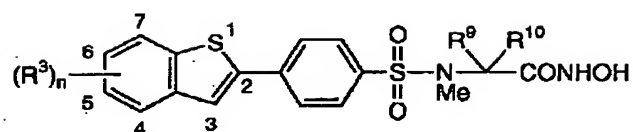


番号	(R ³) _n —	$\begin{array}{c} R^9 \\ \diagup \quad \diagdown \\ R^{10} \end{array}$	番号	(R ³) _n —	$\begin{array}{c} R^9 \\ \diagup \quad \diagdown \\ R^{10} \end{array}$
1 1	6-CH ₃		1 6	5,6-diCH ₃	
1 2	6-CH ₃		1 7	5,6-diCH ₃	
1 3	6-CH ₃		1 8	5,6-diCH ₃	
1 4	6-CH ₃		1 9	5,6-diCH ₃	
1 5	6-CH ₃		2 0	5,6-diCH ₃	

[0053]

[Table 24]

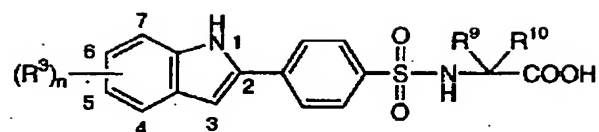
表 8 (つづき)



番号	(R ³) _n —	$\begin{array}{c} \text{R}^9 \quad \text{R}^{10} \\ \diagdown \quad \diagup \\ \text{C} \end{array}$	番号	(R ³) _n —	$\begin{array}{c} \text{R}^9 \quad \text{R}^{10} \\ \diagdown \quad \diagup \\ \text{C} \end{array}$
2 1	5-OCH ₃		2 6	6-OCH ₃	
2 2	5-OCH ₃		2 7	6-OCH ₃	
2 3	5-OCH ₃		2 8	6-OCH ₃	
2 4	5-OCH ₃		2 9	6-OCH ₃	
2 5	5-OCH ₃		3 0	6-OCH ₃	

[0054]
[Table 25]

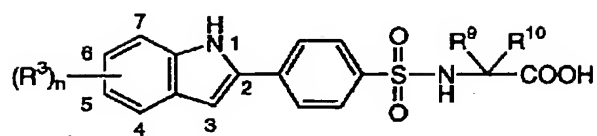
表 9



番号	$(R^3)_n$ —	$\begin{array}{c} R^9 \\ \diagup \quad \diagdown \\ R^{10} \end{array}$	番号	$(R^3)_n$ —	$\begin{array}{c} R^9 \\ \diagup \quad \diagdown \\ R^{10} \end{array}$
1	H		6	5-CH ₃	
2	H		7	5-CH ₃	
3	H		8	5-CH ₃	
4	H		9	5-CH ₃	
5	H		10	5-CH ₃	

[0055]
[Table 26]

表9 (つづき)

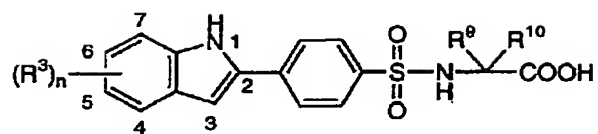


番号	(R³) _n —	$\begin{array}{c} R^9 \\ \diagup \quad \diagdown \\ R^{10} \end{array}$	番号	(R³) _n —	$\begin{array}{c} R^9 \\ \diagup \quad \diagdown \\ R^{10} \end{array}$
1 1	6-CH ₃		1 6	5,6-diCH ₃	
1 2	6-CH ₃		1 7	5,6-diCH ₃	
1 3	6-CH ₃		1 8	5,6-diCH ₃	
1 4	6-CH ₃		1 9	5,6-diCH ₃	
1 5	6-CH ₃		2 0	5,6-diCH ₃	

[0056]

[Table 27]

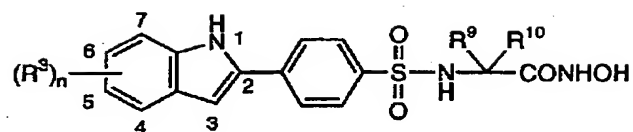
表9 (つづき)



番号	(R³) _n —	$\begin{array}{c} R^9 \\ \diagup \quad \diagdown \\ R^{10} \end{array}$	番号	(R³) _n —	$\begin{array}{c} R^9 \\ \diagup \quad \diagdown \\ R^{10} \end{array}$
2 1	5-OCH ₃		2 6	6-OCH ₃	
2 2	5-OCH ₃		2 7	6-OCH ₃	
2 3	5-OCH ₃		2 8	6-OCH ₃	
2 4	5-OCH ₃		2 9	6-OCH ₃	
2 5	5-OCH ₃		3 0	6-OCH ₃	

[0057]
[Table 28]

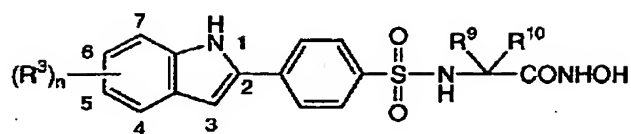
表 10



番号	(R ³) _n —	R ⁹ R ¹⁰	番号	(R ³) _n —	R ⁹ R ¹⁰
1	H		6	5-CH ₃	
2	H		7	5-CH ₃	
3	H		8	5-CH ₃	
4	H		9	5-CH ₃	
5	H		10	5-CH ₃	

[0058]
[Table 29]

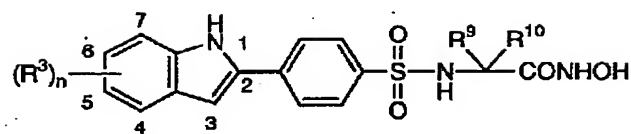
表10 (つづき)



番号	(R ³) _n —	R ⁹ R ¹⁰	番号	(R ³) _n —	R ⁹ R ¹⁰
1 1	6-CH ₃		1 6	5,6-diCH ₃	
1 2	6-CH ₃		1 7	5,6-diCH ₃	
1 3	6-CH ₃		1 8	5,6-diCH ₃	
1 4	6-CH ₃		1 9	5,6-diCH ₃	
1 5	6-CH ₃		2 0	5,6-diCH ₃	

[0059]
[Table 30]

表10 (つづき)

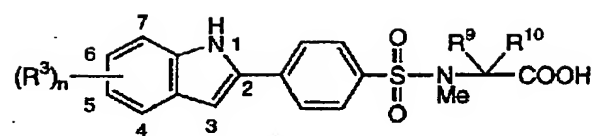


番号	(R³) _n —	R⁹ R¹⁰	番号	(R³) _n —	R⁹ R¹⁰
2 1	5-OCH ₃		2 6	6-OCH ₃	
2 2	5-OCH ₃		2 7	6-OCH ₃	
2 3	5-OCH ₃		2 8	6-OCH ₃	
2 4	5-OCH ₃		2 9	6-OCH ₃	
2 5	5-OCH ₃		3 0	6-OCH ₃	

[0060]

[Table 31]

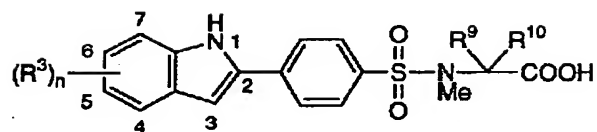
表 1 1



番号	(R ³) _n —	R ⁹ R ¹⁰	番号	(R ³) _n —	R ⁹ R ¹⁰
1	H		6	5-CH ₃	
2	H		7	5-CH ₃	
3	H		8	5-CH ₃	
4	H		9	5-CH ₃	
5	H		10	5-CH ₃	

[0061]
[Table 32]

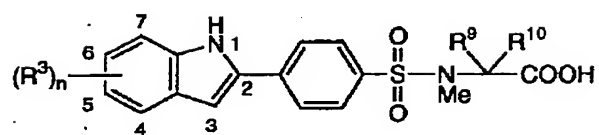
表 11 (つづき)



番号	(R ³) _n —	R ⁹ R ¹⁰	番号	(R ³) _n —	R ⁹ R ¹⁰
1 1	6-CH ₃		1 6	5,6-diCH ₃	
1 2	6-CH ₃		1 7	5,6-diCH ₃	
1 3	6-CH ₃		1 8	5,6-diCH ₃	
1 4	6-CH ₃		1 9	5,6-diCH ₃	
1 5	6-CH ₃		2 0	5,6-diCH ₃	

[0062]
[Table 33]

表 1 1 (つづき)

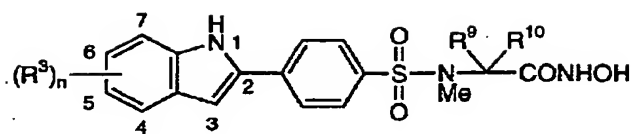


番号	(R ³) _n —	R ⁹ R ¹⁰	番号	(R ³) _n —	R ⁹ R ¹⁰
2 1	5-OCH ₃		2 6	6-OCH ₃	
2 2	5-OCH ₃		2 7	6-OCH ₃	
2 3	5-OCH ₃		2 8	6-OCH ₃	
2 4	5-OCH ₃		2 9	6-OCH ₃	
2 5	5-OCH ₃		3 0	6-OCH ₃	

[0063]

[Table 34]

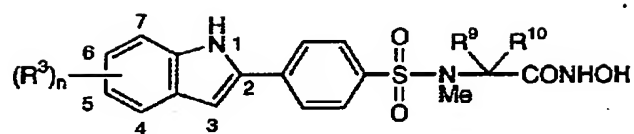
表 1 2



番号	(R ³) _n —	R ⁹ R ¹⁰	番号	(R ³) _n —	R ⁹ R ¹⁰
1	H		6	5-CH ₃	
2	H		7	5-CH ₃	
3	H		8	5-CH ₃	
4	H		9	5-CH ₃	
5	H		10	5-CH ₃	

[0064]
[Table 35]

表 12 (つづき)

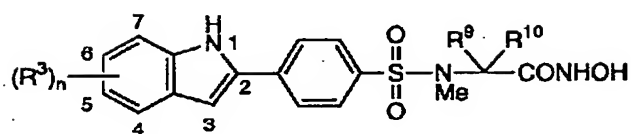


番号	(R ³) _n —	$\begin{array}{c} \text{R}^9 \quad \text{R}^{10} \\ \diagdown \quad \diagup \\ \text{C} \end{array}$	番号	(R ³) _n —	$\begin{array}{c} \text{R}^9 \quad \text{R}^{10} \\ \diagdown \quad \diagup \\ \text{C} \end{array}$
1 1	6-CH ₃		1 6	5,6-diCH ₃	
1 2	6-CH ₃		1 7	5,6-diCH ₃	
1 3	6-CH ₃		1 8	5,6-diCH ₃	
1 4	6-CH ₃		1 9	5,6-diCH ₃	
1 5	6-CH ₃		2 0	5,6-diCH ₃	

[0065]

[Table 36]

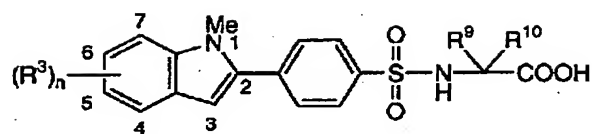
表12 (つづき)



番号	(R³) _n —	R⁹ R¹⁰	番号	(R³) _n —	R⁹ R¹⁰
2 1	5-OCH ₃		2 6	6-OCH ₃	
2 2	5-OCH ₃		2 7	6-OCH ₃	
2 3	5-OCH ₃		2 8	6-OCH ₃	
2 4	5-OCH ₃		2 9	6-OCH ₃	
2 5	5-OCH ₃		3 0	6-OCH ₃	

[0066]
[Table 37]

表 1 3

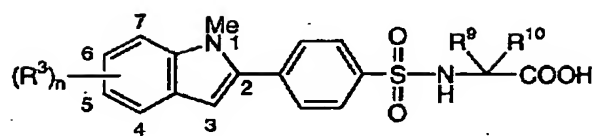


番号	(R ³) _n —	R ⁹ R ¹⁰	番号	(R ³) _n —	R ⁹ R ¹⁰
1	H		6	5-CH ₃	
2	H		7	5-CH ₃	
3	H		8	5-CH ₃	
4	H		9	5-CH ₃	
5	H		10	5-CH ₃	

[0067]

[Table 38]

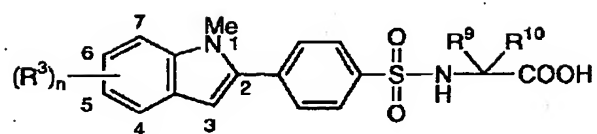
表 13 (つづき)



番号	(R ³) _n —	R ⁹ R ¹⁰	番号	(R ³) _n —	R ⁹ R ¹⁰
1 1	6-CH ₃		1 6	5,6-diCH ₃	
1 2	6-CH ₃		1 7	5,6-diCH ₃	
1 3	6-CH ₃		1 8	5,6-diCH ₃	
1 4	6-CH ₃		1 9	5,6-diCH ₃	
1 5	6-CH ₃		2 0	5,6-diCH ₃	

[0068]
[Table 39]

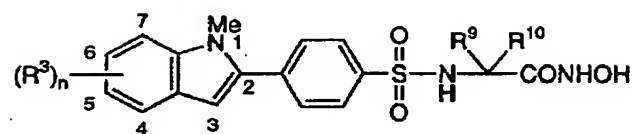
表 13. (つづき)



番号	(R ³) _n —	R ⁹ R ¹⁰	番号	(R ³) _n —	R ⁹ R ¹⁰
2 1	5-OCH ₃		2 6	6-OCH ₃	
2 2	5-OCH ₃		2 7	6-OCH ₃	
2 3	5-OCH ₃		2 8	6-OCH ₃	
2 4	5-OCH ₃		2 9	6-OCH ₃	
2 5	5-OCH ₃		3 0	6-OCH ₃	

[0069]
[Table 40]

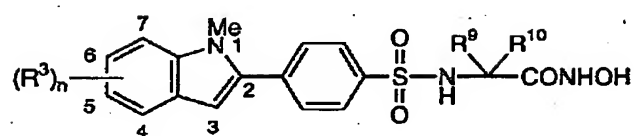
表 1 4



番号	(R ³) _n —	R ⁹ R ¹⁰	番号	(R ³) _n —	R ⁹ R ¹⁰
1	H		6	5-CH ₃	
2	H		7	5-CH ₃	
3	H		8	5-CH ₃	
4	H		9	5-CH ₃	
5	H		10	5-CH ₃	

[0070]
[Table 41]

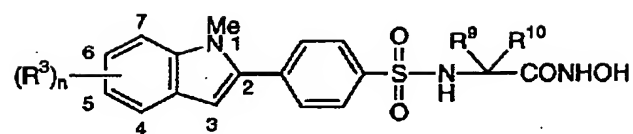
表14 (つづき)



番号	(R ³) _n —	R ⁹ R ¹⁰	番号	(R ³) _n —	R ⁹ R ¹⁰
1 1	6-CH ₃		1 6	5,6-diCH ₃	
1 2	6-CH ₃		1 7	5,6-diCH ₃	
1 3	6-CH ₃		1 8	5,6-diCH ₃	
1 4	6-CH ₃		1 9	5,6-diCH ₃	
1 5	6-CH ₃		2 0	5,6-diCH ₃	

[0071]
[Table 42]

表 1 4 (つづき)

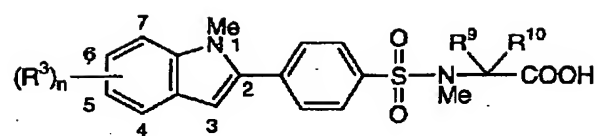


番号	(R ³) _n —	$\begin{array}{c} \text{R}^9 \quad \text{R}^{10} \\ \diagdown \quad \diagup \\ \text{C} \end{array}$	番号	(R ³) _n —	$\begin{array}{c} \text{R}^9 \quad \text{R}^{10} \\ \diagdown \quad \diagup \\ \text{C} \end{array}$
2 1	5-OCH ₃		2 6	6-OCH ₃	
2 2	5-OCH ₃		2 7	6-OCH ₃	
2 3	5-OCH ₃		2 8	6-OCH ₃	
2 4	5-OCH ₃		2 9	6-OCH ₃	
2 5	5-OCH ₃		3 0	6-OCH ₃	

[0072]

[Table 43]

表 1 5

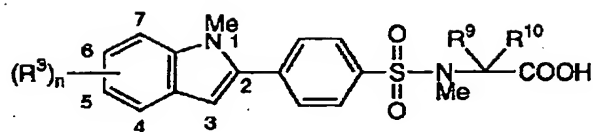


番号	(R ³) _n —	$\begin{matrix} R^9 & R^{10} \\ \diagdown & / \\ & \end{matrix}$	番号	(R ³) _n —	$\begin{matrix} R^9 & R^{10} \\ \diagdown & / \\ & \end{matrix}$
1	H		6	5-CH ₃	
2	H		7	5-CH ₃	
3	H		8	5-CH ₃	
4	H		9	5-CH ₃	
5	H		10	5-CH ₃	

[0073]

[Table 44]

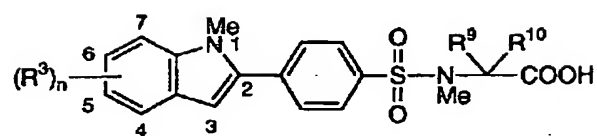
表15 (つづき)



番号	(R ³) _n —	R ⁹ R ¹⁰	番号	(R ³) _n —	R ⁹ R ¹⁰
1 1	6-CH ₃		1 6	5,6-diCH ₃	
1 2	6-CH ₃		1 7	5,6-diCH ₃	
1 3	6-CH ₃		1 8	5,6-diCH ₃	
1 4	6-CH ₃		1 9	5,6-diCH ₃	
1 5	6-CH ₃		2 0	5,6-diCH ₃	

[0074]
[Table 45]

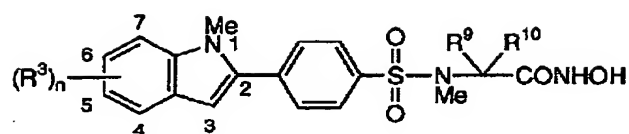
表 1 5 (つづき)



番号	(R ³) _n —	R ⁹ R ¹⁰	番号	(R ³) _n —	R ⁹ R ¹⁰
2 1	5-OCH ₃		2 6	6-OCH ₃	
2 2	5-OCH ₃		2 7	6-OCH ₃	
2 3	5-OCH ₃		2 8	6-OCH ₃	
2 4	5-OCH ₃		2 9	6-OCH ₃	
2 5	5-OCH ₃		3 0	6-OCH ₃	

[0075]
[Table 46]

表 1 6

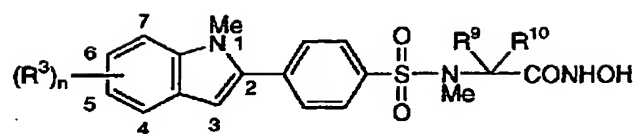


番号	(R ³) _n —	R ⁹ R ¹⁰	番号	(R ³) _n —	R ⁹ R ¹⁰
1	H		6	5-CH ₃	
2	H		7	5-CH ₃	
3	H		8	5-CH ₃	
4	H		9	5-CH ₃	
5	H		10	5-CH ₃	

[0076]

[Table 47]

表 16 (つづき)

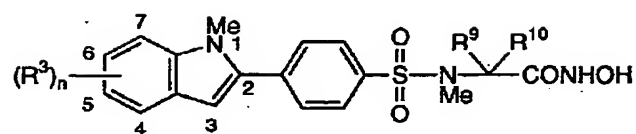


番号	(R ³) _n —	$\begin{array}{c} \text{R}^9 \quad \text{R}^{10} \\ \diagdown \quad \diagup \\ \text{C} \end{array}$	番号	(R ³) _n —	$\begin{array}{c} \text{R}^9 \quad \text{R}^{10} \\ \diagdown \quad \diagup \\ \text{C} \end{array}$
1 1	6-CH ₃		1 6	5,6-diCH ₃	
1 2	6-CH ₃		1 7	5,6-diCH ₃	
1 3	6-CH ₃		1 8	5,6-diCH ₃	
1 4	6-CH ₃		1 9	5,6-diCH ₃	
1 5	6-CH ₃		2 0	5,6-diCH ₃	

[0077]

[Table 48]

表 1 6 (つづき)

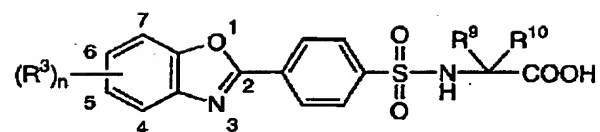


番号	(R ³) _n —	$\begin{array}{c} R^9 \\ \diagup \quad \diagdown \\ R^9 \quad R^{10} \end{array}$	番号	(R ³) _n —	$\begin{array}{c} R^9 \\ \diagup \quad \diagdown \\ R^9 \quad R^{10} \end{array}$
2 1	5-OCH ₃		2 6	6-OCH ₃	
2 2	5-OCH ₃		2 7	6-OCH ₃	
2 3	5-OCH ₃		2 8	6-OCH ₃	
2 4	5-OCH ₃		2 9	6-OCH ₃	
2 5	5-OCH ₃		3 0	6-OCH ₃	

[0078]

[Table 49]

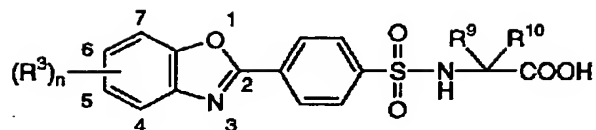
表 17



番号	(R ³) _n —	R ⁹ R ¹⁰	番号	(R ³) _n —	R ⁹ R ¹⁰
1	H		6	5-CH ₃	
2	H		7	5-CH ₃	
3	H		8	5-CH ₃	
4	H		9	5-CH ₃	
5	H		10	5-CH ₃	

[0079]
[Table 50]

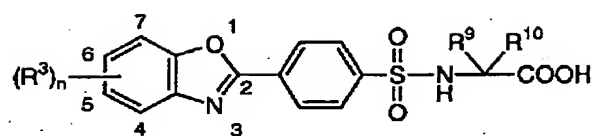
表17 (つづき)



番号	(R ³) _n —	$\begin{array}{c} \text{R}^9 \\ \diagup \quad \diagdown \\ \text{R}^{10} \end{array}$	番号	(R ³) _n —	$\begin{array}{c} \text{R}^9 \\ \diagup \quad \diagdown \\ \text{R}^{10} \end{array}$
1 1	6-CH ₃		1 6	5,6-diCH ₃	
1 2	6-CH ₃		1 7	5,6-diCH ₃	
1 3	6-CH ₃		1 8	5,6-diCH ₃	
1 4	6-CH ₃		1 9	5,6-diCH ₃	
1 5	6-CH ₃		2 0	5,6-diCH ₃	

[0080]
[Table 51]

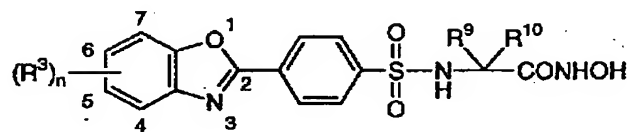
表17 (つづき)



番号	(R³) _n —	R⁹R¹⁰	番号	(R³) _n —	R⁹R¹⁰
2 1	5-OCH ₃		2 6	6-OCH ₃	
2 2	5-OCH ₃		2 7	6-OCH ₃	
2 3	5-OCH ₃		2 8	6-OCH ₃	
2 4	5-OCH ₃		2 9	6-OCH ₃	
2 5	5-OCH ₃		3 0	6-OCH ₃	

[0081]
[Table 52]

表 18

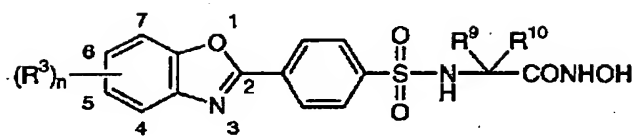


番号	(R ³) _n —	R ⁹ R ¹⁰	番号	(R ³) _n —	R ⁹ R ¹⁰
1	H		6	5-CH ₃	
2	H		7	5-CH ₃	
3	H		8	5-CH ₃	
4	H		9	5-CH ₃	
5	H		10	5-CH ₃	

[0082]

[Table 53]

表 18 (つづき)

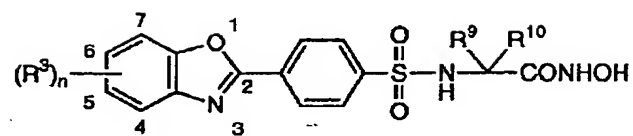


番号	(R³) _n —	$\begin{array}{c} R^9 \\ \diagup \quad \diagdown \\ R^{10} \end{array}$	番号	(R³) _n —	$\begin{array}{c} R^9 \\ \diagup \quad \diagdown \\ R^{10} \end{array}$
1 1	6-CH ₃		1 6	5,6-diCH ₃	
1 2	6-CH ₃		1 7	5,6-diCH ₃	
1 3	6-CH ₃		1 8	5,6-diCH ₃	
1 4	6-CH ₃		1 9	5,6-diCH ₃	
1 5	6-CH ₃		2 0	5,6-diCH ₃	

[0083]

[Table 54]

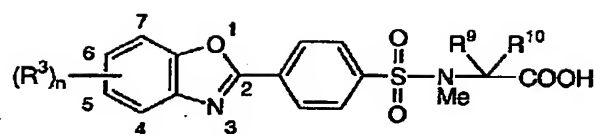
表 18 (つづき)



番号	(R³) _n —	$\begin{array}{c} \text{R}^9 \quad \text{R}^{10} \\ \diagdown \quad \diagup \\ \text{C} \end{array}$	番号	(R³) _n —	$\begin{array}{c} \text{R}^9 \quad \text{R}^{10} \\ \diagdown \quad \diagup \\ \text{C} \end{array}$
2 1	5-OCH ₃		2 6	6-OCH ₃	
2 2	5-OCH ₃		2 7	6-OCH ₃	
2 3	5-OCH ₃		2 8	6-OCH ₃	
2 4	5-OCH ₃		2 9	6-OCH ₃	
2 5	5-OCH ₃		3 0	6-OCH ₃	

[0084]
[Table 55]

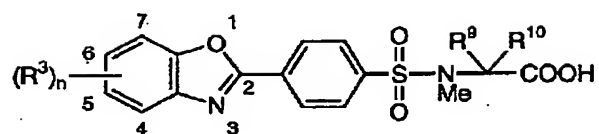
表 19



番号	(R ³) _n —	R ⁹ R ¹⁰	番号	(R ³) _n —	R ⁹ R ¹⁰
1	H		6	5-CH ₃	
2	H		7	5-CH ₃	
3	H		8	5-CH ₃	
4	H		9	5-CH ₃	
5	H		10	5-CH ₃	

[0085]
[Table 56]

表19 (つづき)

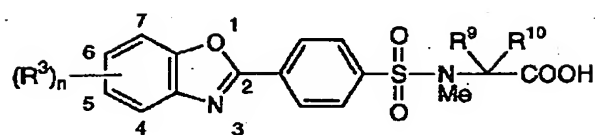


番号	(R³) _n —	$\begin{array}{c} R^9 \\ \diagup \quad \diagdown \\ R^{10} \end{array}$	番号	(R³) _n —	$\begin{array}{c} R^9 \\ \diagup \quad \diagdown \\ R^{10} \end{array}$
11	6-CH ₃		16	5,6-diCH ₃	
12	6-CH ₃		17	5,6-diCH ₃	
13	6-CH ₃		18	5,6-diCH ₃	
14	6-CH ₃		19	5,6-diCH ₃	
15	6-CH ₃		20	5,6-diCH ₃	

[0086]

[Table 57]

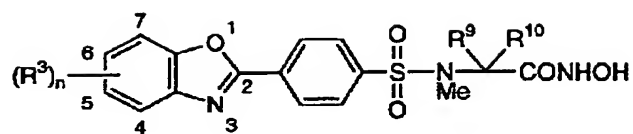
表 19 (つづき)



番号	(R ³) _n —	R ⁹ R ¹⁰	番号	(R ³) _n —	R ⁹ R ¹⁰
2 1	5-OCH ₃		2 6	6-OCH ₃	
2 2	5-OCH ₃		2 7	6-OCH ₃	
2 3	5-OCH ₃		2 8	6-OCH ₃	
2 4	5-OCH ₃		2 9	6-OCH ₃	
2 5	5-OCH ₃		3 0	6-OCH ₃	

[0087]
[Table 58]

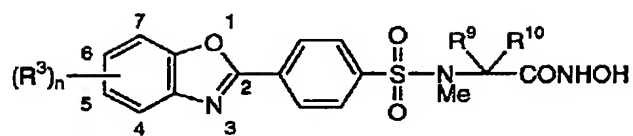
表 2 0



番号	(R ³) _n —	R ⁹ R ¹⁰	番号	(R ³) _n —	R ⁹ R ¹⁰
1	H		6	5-CH ₃	
2	H		7	5-CH ₃	
3	H		8	5-CH ₃	
4	H		9	5-CH ₃	
5	H		10	5-CH ₃	

[0088]
[Table 59]

表 20 (つづき)

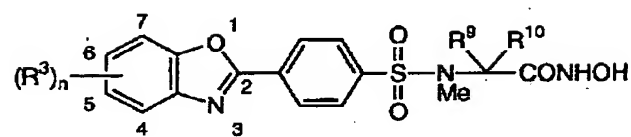


番号	(R ³) _n —	R ⁹ R ¹⁰	番号	(R ³) _n —	R ⁹ R ¹⁰
1 1	6-CH ₃		1 6	5,6-diCH ₃	
1 2	6-CH ₃		1 7	5,6-diCH ₃	
1 3	6-CH ₃		1 8	5,6-diCH ₃	
1 4	6-CH ₃		1 9	5,6-diCH ₃	
1 5	6-CH ₃		2 0	5,6-diCH ₃	

[0089]

[Table 60]

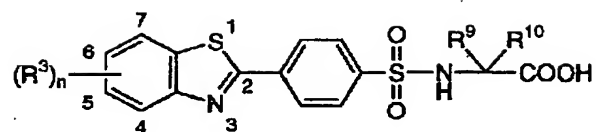
表20 (つづき)



番号	(R ³) _n —	$\begin{array}{c} \text{R}^9 \quad \text{R}^{10} \\ \diagdown \quad \diagup \\ \text{C} \end{array}$	番号	(R ³) _n —	$\begin{array}{c} \text{R}^9 \quad \text{R}^{10} \\ \diagdown \quad \diagup \\ \text{C} \end{array}$
2 1	5-OCH ₃		2 6	6-OCH ₃	
2 2	5-OCH ₃		2 7	6-OCH ₃	
2 3	5-OCH ₃		2 8	6-OCH ₃	
2 4	5-OCH ₃		2 9	6-OCH ₃	
2 5	5-OCH ₃		3 0	6-OCH ₃	

[0090]
[Table 61]

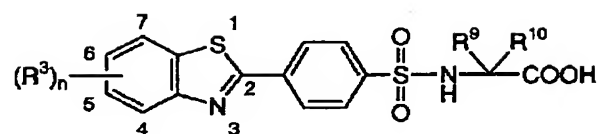
表 2 1



番号	(R ³) _n —	R ⁹ R ¹⁰	番号	(R ³) _n —	R ⁹ R ¹⁰
1	H		6	5-CH ₃	
2	H		7	5-CH ₃	
3	H		8	5-CH ₃	
4	H		9	5-CH ₃	
5	H		10	5-CH ₃	

[0091]
[Table 62]

表 2 1 (つづき)

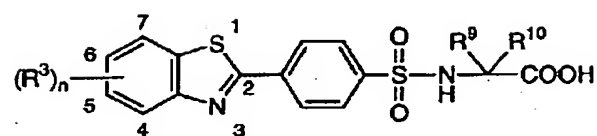


番号	(R³) _n —	$\begin{array}{c} R^9 \\ \diagup \quad \diagdown \\ R^{10} \end{array}$	番号	(R³) _n —	$\begin{array}{c} R^9 \\ \diagup \quad \diagdown \\ R^{10} \end{array}$
1 1	6-CH ₃		1 6	5,6-diCH ₃	
1 2	6-CH ₃		1 7	5,6-diCH ₃	
1 3	6-CH ₃		1 8	5,6-diCH ₃	
1 4	6-CH ₃		1 9	5,6-diCH ₃	
1 5	6-CH ₃		2 0	5,6-diCH ₃	

[0092]

[Table 63]

表 2 1 (つづき)

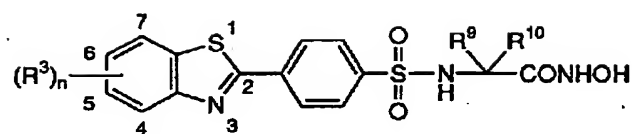


番号	(R ³) _n —	R ⁹ R ¹⁰	番号	(R ³) _n —	R ⁹ R ¹⁰
2 1	5-OCH ₃		2 6	6-OCH ₃	
2 2	5-OCH ₃		2 7	6-OCH ₃	
2 3	5-OCH ₃		2 8	6-OCH ₃	
2 4	5-OCH ₃		2 9	6-OCH ₃	
2 5	5-OCH ₃		3 0	6-OCH ₃	

[0093]

[Table 64]

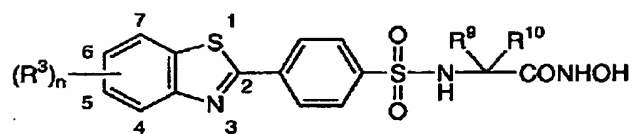
表 2 2



番号	(R³) _n —	R⁹ R¹⁰	番号	(R³) _n —	R⁹ R¹⁰
1	H		6	5-CH₃	
2	H		7	5-CH₃	
3	H		8	5-CH₃	
4	H		9	5-CH₃	
5	H		10	5-CH₃	

[0094]
[Table 65]

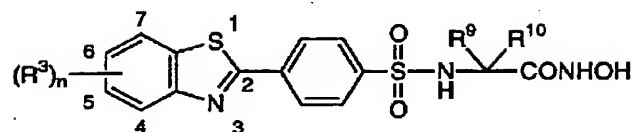
表 2 2 (つづき)



番号	(R³) _n —	$\begin{array}{c} \text{R}^9 \quad \text{R}^{10} \\ \diagdown \quad \diagup \\ \text{CH} \end{array}$	番号	(R³) _n —	$\begin{array}{c} \text{R}^9 \quad \text{R}^{10} \\ \diagdown \quad \diagup \\ \text{CH} \end{array}$
1 1	6-CH ₃		1 6	5,6-diCH ₃	
1 2	6-CH ₃		1 7	5,6-diCH ₃	
1 3	6-CH ₃		1 8	5,6-diCH ₃	
1 4	6-CH ₃		1 9	5,6-diCH ₃	
1 5	6-CH ₃		2 0	5,6-diCH ₃	

[0095]
[Table 66]

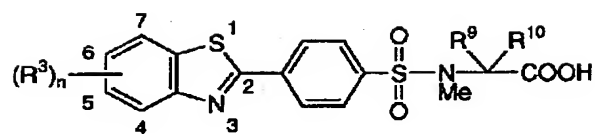
表 2 2 (つづき)



番号	(R³) _n —	R⁹ R¹⁰	番号	(R³) _n —	R⁹ R¹⁰
2 1	5-OCH ₃		2 6	6-OCH ₃	
2 2	5-OCH ₃		2 7	6-OCH ₃	
2 3	5-OCH ₃		2 8	6-OCH ₃	
2 4	5-OCH ₃		2 9	6-OCH ₃	
2 5	5-OCH ₃		3 0	6-OCH ₃	

[0096]
[Table 67]

表 2 3

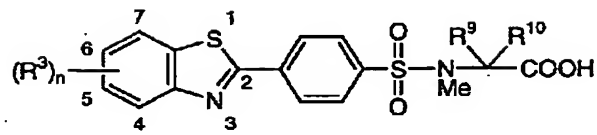


番号	(R³) _n —	$\begin{array}{c} \text{R}^9 \quad \text{R}^{10} \\ \diagdown \quad \diagup \\ \text{C} \end{array}$	番号	(R³) _n —	$\begin{array}{c} \text{R}^9 \quad \text{R}^{10} \\ \diagdown \quad \diagup \\ \text{C} \end{array}$
1	H		6	5-CH ₃	
2	H		7	5-CH ₃	
3	H		8	5-CH ₃	
4	H		9	5-CH ₃	
5	H		10	5-CH ₃	

[0097]

[Table 68]

表 2 3 (つづき)

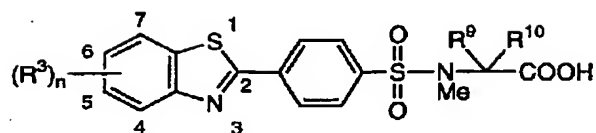


番号	(R³) _n —	$\begin{array}{c} \text{R}^9 \quad \text{R}^{10} \\ \diagdown \quad \diagup \\ \text{C} \end{array}$	番号	(R³) _n —	$\begin{array}{c} \text{R}^9 \quad \text{R}^{10} \\ \diagdown \quad \diagup \\ \text{C} \end{array}$
1 1	6-CH ₃		1 6	5,6-diCH ₃	
1 2	6-CH ₃		1 7	5,6-diCH ₃	
1 3	6-CH ₃		1 8	5,6-diCH ₃	
1 4	6-CH ₃		1 9	5,6-diCH ₃	
1 5	6-CH ₃		2 0	5,6-diCH ₃	

[0098]

[Table 69]

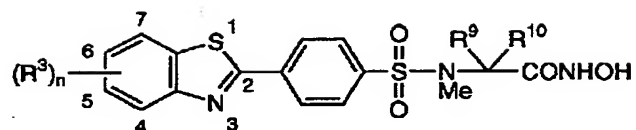
表 2 3 (つづき)



番号	(R ³) _n —	R ⁹ R ¹⁰	番号	(R ³) _n —	R ⁹ R ¹⁰
2 1	5-OCH ₃		2 6	6-OCH ₃	
2 2	5-OCH ₃		2 7	6-OCH ₃	
2 3	5-OCH ₃		2 8	6-OCH ₃	
2 4	5-OCH ₃		2 9	6-OCH ₃	
2 5	5-OCH ₃		3 0	6-OCH ₃	

[0099]
[Table 70]

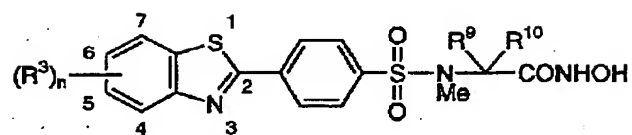
表 2 4



番号	(R ³) _n —	R ⁹ R ¹⁰	番号	(R ³) _n —	R ⁹ R ¹⁰
1	H		6	5-CH ₃	
2	H		7	5-CH ₃	
3	H		8	5-CH ₃	
4	H		9	5-CH ₃	
5	H		10	5-CH ₃	

[0100]
[Table 71]

表 2 4 (つづき)

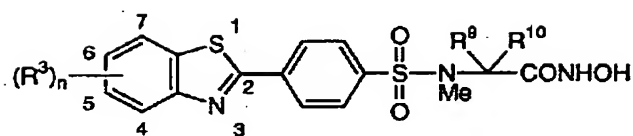


番号	(R ³) _n —	R ⁹ R ¹⁰	番号	(R ³) _n —	R ⁹ R ¹⁰
1 1	6-CH ₃		1 6	5,6-diCH ₃	
1 2	6-CH ₃		1 7	5,6-diCH ₃	
1 3	6-CH ₃		1 8	5,6-diCH ₃	
1 4	6-CH ₃		1 9	5,6-diCH ₃	
1 5	6-CH ₃		2 0	5,6-diCH ₃	

[0101]

[Table 72]

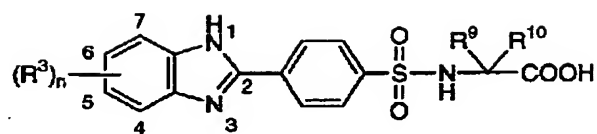
表 2 4 (つづき)



番号	(R ³) _n —	$\begin{array}{c} \text{R}^9 \quad \text{R}^{10} \\ \diagdown \quad \diagup \\ \text{C} \end{array}$	番号	(R ³) _n —	$\begin{array}{c} \text{R}^9 \quad \text{R}^{10} \\ \diagdown \quad \diagup \\ \text{C} \end{array}$
2 1	5-OCH ₃		2 6	6-OCH ₃	
2 2	5-OCH ₃		2 7	6-OCH ₃	
2 3	5-OCH ₃		2 8	6-OCH ₃	
2 4	5-OCH ₃		2 9	6-OCH ₃	
2 5	5-OCH ₃		3 0	6-OCH ₃	

[0102]
[Table 73]

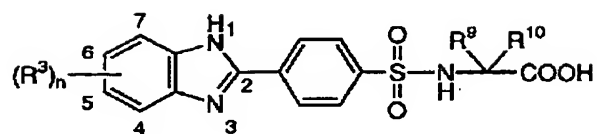
表 2 5



番号	(R³) _n —	$\begin{array}{c} \text{R}^9 \quad \text{R}^{10} \\ \diagdown \quad \diagup \\ \text{C} \end{array}$	番号	(R³) _n —	$\begin{array}{c} \text{R}^9 \quad \text{R}^{10} \\ \diagdown \quad \diagup \\ \text{C} \end{array}$
1	H		6	5-CH ₃	
2	H		7	5-CH ₃	
3	H		8	5-CH ₃	
4	H		9	5-CH ₃	
5	H		10	5-CH ₃	

[0103]
[Table 74]

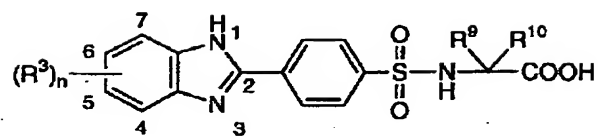
表 2 5 (つづき)



番号	(R³) _n —	$\begin{array}{c} R^9 \\ \diagup \quad \diagdown \\ R^{10} \end{array}$	番号	(R³) _n —	$\begin{array}{c} R^9 \\ \diagup \quad \diagdown \\ R^{10} \end{array}$
1 1	6-CH ₃		1 6	5,6-diCH ₃	
1 2	6-CH ₃		1 7	5,6-diCH ₃	
1 3	6-CH ₃		1 8	5,6-diCH ₃	
1 4	6-CH ₃		1 9	5,6-diCH ₃	
1 5	6-CH ₃		2 0	5,6-diCH ₃	

[0104]
[Table 75]

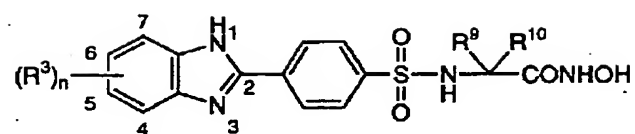
表 2 5 (つづき)



番号	(R ³) _n —	$\begin{array}{c} \text{R}^9 \quad \text{R}^{10} \\ \diagdown \quad \diagup \\ \text{C}^* \end{array}$	番号	(R ³) _n —	$\begin{array}{c} \text{R}^9 \quad \text{R}^{10} \\ \diagdown \quad \diagup \\ \text{C}^* \end{array}$
2 1	5-OCH ₃		2 6	6-OCH ₃	
2 2	5-OCH ₃		2 7	6-OCH ₃	
2 3	5-OCH ₃		2 8	6-OCH ₃	
2 4	5-OCH ₃		2 9	6-OCH ₃	
2 5	5-OCH ₃		3 0	6-OCH ₃	

[0105]
[Table 76]

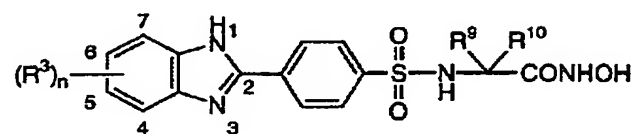
表 2 6



番号	(R³) _n —	$\begin{array}{c} R^9 \\ \diagup \quad \diagdown \\ R^{10} \end{array}$	番号	(R³) _n —	$\begin{array}{c} R^9 \\ \diagup \quad \diagdown \\ R^{10} \end{array}$
1	H		6	5-CH ₃	
2	H		7	5-CH ₃	
3	H		8	5-CH ₃	
4	H		9	5-CH ₃	
5	H		10	5-CH ₃	

[0106]
[Table 77]

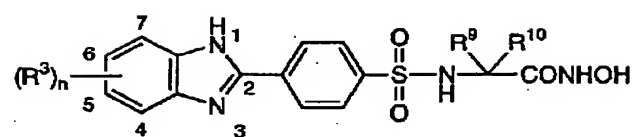
表 2 6 (つづき)



番号	(R ³) _n —	R ⁹ R ¹⁰	番号	(R ³) _n —	R ⁹ R ¹⁰
1 1	6-CH ₃		1 6	5,6-diCH ₃	
1 2	6-CH ₃		1 7	5,6-diCH ₃	
1 3	6-CH ₃		1 8	5,6-diCH ₃	
1 4	6-CH ₃		1 9	5,6-diCH ₃	
1 5	6-CH ₃		2 0	5,6-diCH ₃	

[0107]
[Table 78]

表 2 6 (つづき)

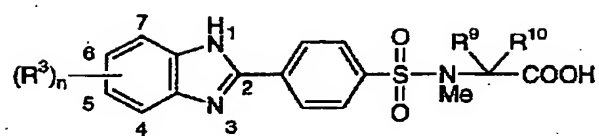


番号	(R ³) _n —	$\begin{array}{c} \text{R}^9 \quad \text{R}^{10} \\ \diagdown \quad \diagup \\ \text{C} \end{array}$	番号	(R ³) _n —	$\begin{array}{c} \text{R}^9 \quad \text{R}^{10} \\ \diagdown \quad \diagup \\ \text{C} \end{array}$
2 1	5-OCH ₃		2 6	6-OCH ₃	
2 2	5-OCH ₃		2 7	6-OCH ₃	
2 3	5-OCH ₃		2 8	6-OCH ₃	
2 4	5-OCH ₃		2 9	6-OCH ₃	
2 5	5-OCH ₃		3 0	6-OCH ₃	

[0108]

[Table 79]

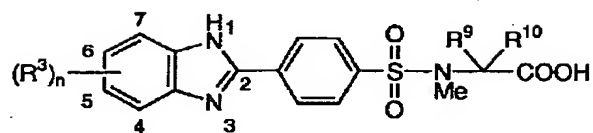
表 2 7



番号	(R ³) _n —	$\begin{array}{c} \text{R}^9 \quad \text{R}^{10} \\ \diagdown \quad \diagup \\ \text{C} \end{array}$	番号	(R ³) _n —	$\begin{array}{c} \text{R}^9 \quad \text{R}^{10} \\ \diagdown \quad \diagup \\ \text{C} \end{array}$
1	H		6	5-CH ₃	
2	H		7	5-CH ₃	
3	H		8	5-CH ₃	
4	H		9	5-CH ₃	
5	H		10	5-CH ₃	

[0109]
[Table 80]

表 27 (つづき)

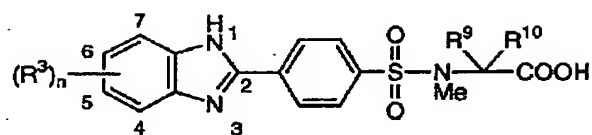


番号	(R ³) _n —	$\begin{array}{c} \text{R}^9 \quad \text{R}^{10} \\ \diagdown \quad \diagup \\ \text{C} \end{array}$	番号	(R ³) _n —	$\begin{array}{c} \text{R}^9 \quad \text{R}^{10} \\ \diagdown \quad \diagup \\ \text{C} \end{array}$
1 1	6-CH ₃		1 6	5,6-diCH ₃	
1 2	6-CH ₃		1 7	5,6-diCH ₃	
1 3	6-CH ₃		1 8	5,6-diCH ₃	
1 4	6-CH ₃		1 9	5,6-diCH ₃	
1 5	6-CH ₃		2 0	5,6-diCH ₃	

[0110]

[Table 81]

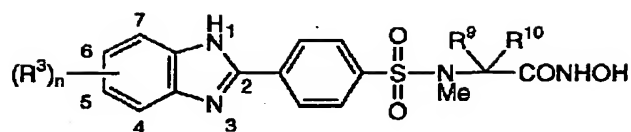
表 2 7 (つづき)



番号	(R ³) _n —	$\begin{array}{c} \text{R}^9 \quad \text{R}^{10} \\ \diagdown \quad \diagup \\ \text{C} \end{array}$	番号	(R ³) _n —	$\begin{array}{c} \text{R}^9 \quad \text{R}^{10} \\ \diagdown \quad \diagup \\ \text{C} \end{array}$
2 1	5-OCH ₃		2 6	6-OCH ₃	
2 2	5-OCH ₃		2 7	6-OCH ₃	
2 3	5-OCH ₃		2 8	6-OCH ₃	
2 4	5-OCH ₃		2 9	6-OCH ₃	
2 5	5-OCH ₃		3 0	6-OCH ₃	

[0111]
[Table 82]

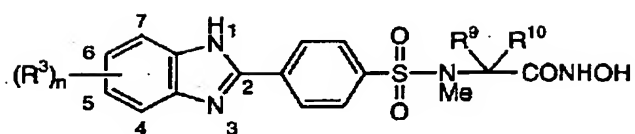
表 2 8



番号	(R³) _n —	$\begin{array}{c} \text{R}^9 \quad \text{R}^{10} \\ \diagdown \quad \diagup \\ \text{C} \end{array}$	番号	(R³) _n —	$\begin{array}{c} \text{R}^9 \quad \text{R}^{10} \\ \diagdown \quad \diagup \\ \text{C} \end{array}$
1	H		6	5-CH ₃	
2	H		7	5-CH ₃	
3	H		8	5-CH ₃	
4	H		9	5-CH ₃	
5	H		10	5-CH ₃	

[0112]
[Table 83]

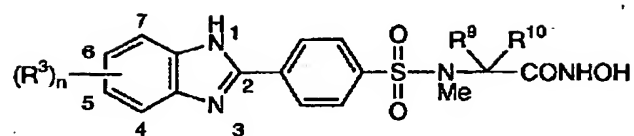
表 2 8 (つづき)



番号	$(R^3)_n$ —	$R^9 R^{10}$	番号	$(R^3)_n$ —	$R^9 R^{10}$
1 1	6-CH ₃		1 6	5,6-diCH ₃	
1 2	6-CH ₃		1 7	5,6-diCH ₃	
1 3	6-CH ₃		1 8	5,6-diCH ₃	
1 4	6-CH ₃		1 9	5,6-diCH ₃	
1 5	6-CH ₃		2 0	5,6-diCH ₃	

[0113]
[Table 84]

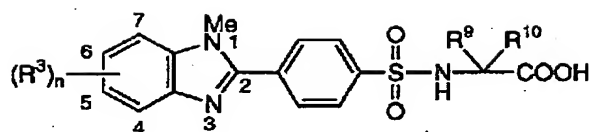
表 2 8 (つづき)



番号	(R³) _n —	$\begin{array}{c} R^9 \\ \diagup \quad \diagdown \\ R^{10} \end{array}$	番号	(R³) _n —	$\begin{array}{c} R^9 \\ \diagup \quad \diagdown \\ R^{10} \end{array}$
2 1	5-OCH ₃		2 6	6-OCH ₃	
2 2	5-OCH ₃		2 7	6-OCH ₃	
2 3	5-OCH ₃		2 8	6-OCH ₃	
2 4	5-OCH ₃		2 9	6-OCH ₃	
2 5	5-OCH ₃		3 0	6-OCH ₃	

[0114]
[Table 85]

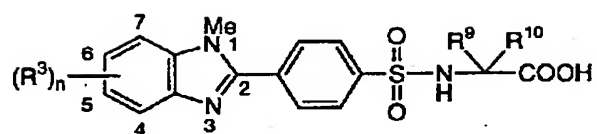
表 2 9



番号	(R ³) _n —	R ⁹ R ¹⁰	番号	(R ³) _n —	R ⁹ R ¹⁰
1	H		6	5-CH ₃	
2	H		7	5-CH ₃	
3	H		8	5-CH ₃	
4	H		9	5-CH ₃	
5	H		10	5-CH ₃	

[0115]
[Table 86]

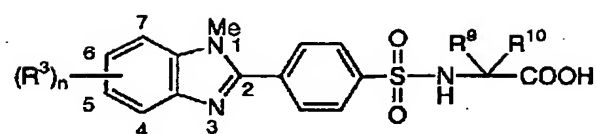
表29 (つづき)



番号	(R ³) _n —	$\begin{array}{c} \text{R}^9 \quad \text{R}^{10} \\ \diagdown \quad \diagup \\ \text{C} \end{array}$	番号	(R ³) _n —	$\begin{array}{c} \text{R}^9 \quad \text{R}^{10} \\ \diagdown \quad \diagup \\ \text{C} \end{array}$
11	6-CH ₃		16	5,6-diCH ₃	
12	6-CH ₃		17	5,6-diCH ₃	
13	6-CH ₃		18	5,6-diCH ₃	
14	6-CH ₃		19	5,6-diCH ₃	
15	6-CH ₃		20	5,6-diCH ₃	

[0116]
[Table 87]

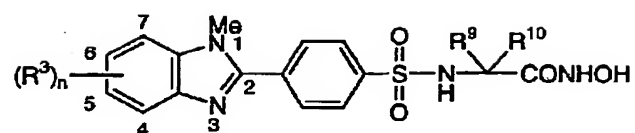
表 2 9 (つづき)



番号	(R ³) _n —	$\begin{array}{c} \text{R}^9 \quad \text{R}^{10} \\ \diagdown \quad \diagup \\ \text{C} \end{array}$	番号	(R ³) _n —	$\begin{array}{c} \text{R}^9 \quad \text{R}^{10} \\ \diagdown \quad \diagup \\ \text{C} \end{array}$
2 1	5-OCH ₃		2 6	6-OCH ₃	
2 2	5-OCH ₃		2 7	6-OCH ₃	
2 3	5-OCH ₃		2 8	6-OCH ₃	
2 4	5-OCH ₃		2 9	6-OCH ₃	
2 5	5-OCH ₃		3 0	6-OCH ₃	

[0117]
[Table 88]

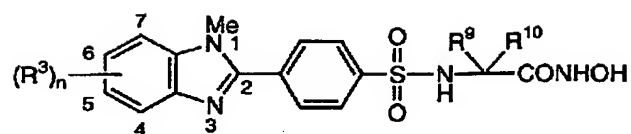
表 3 0



番号	(R ³) _n —	R ⁹ R ¹⁰	番号	(R ³) _n —	R ⁹ R ¹⁰
1	H		6	5-CH ₃	
2	H		7	5-CH ₃	
3	H		8	5-CH ₃	
4	H		9	5-CH ₃	
5	H		10	5-CH ₃	

[0118]
[Table 89]

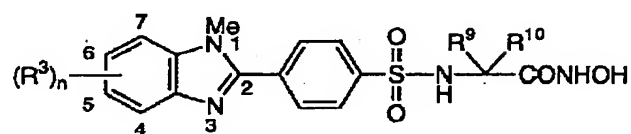
表30 (つづき)



番号	(R³) _n —	R⁹ R¹⁰	番号	(R³) _n —	R⁹ R¹⁰
1 1	6-CH₃		1 6	5,6-diCH₃	
1 2	6-CH₃		1 7	5,6-diCH₃	
1 3	6-CH₃		1 8	5,6-diCH₃	
1 4	6-CH₃		1 9	5,6-diCH₃	
1 5	6-CH₃		2 0	5,6-diCH₃	

[0119]
[Table 90]

表30 (つづき)

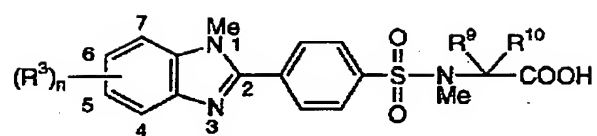


番号	(R ³) _n —	R ⁹ R ¹⁰	番号	(R ³) _n —	R ⁹ R ¹⁰
2 1	5-OCH ₃		2 6	6-OCH ₃	
2 2	5-OCH ₃		2 7	6-OCH ₃	
2 3	5-OCH ₃		2 8	6-OCH ₃	
2 4	5-OCH ₃		2 9	6-OCH ₃	
2 5	5-OCH ₃		3 0	6-OCH ₃	

[0120]

[Table 91]

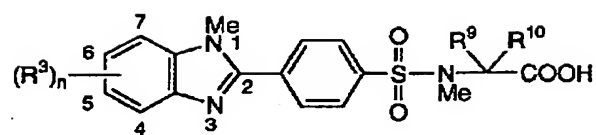
表 3 1



番号	(R ³) _n —	R ⁹ R ¹⁰	番号	(R ³) _n —	R ⁹ R ¹⁰
1	H		6	5-CH ₃	
2	H		7	5-CH ₃	
3	H		8	5-CH ₃	
4	H		9	5-CH ₃	
5	H		10	5-CH ₃	

[0121]
[Table 92]

表 3 1 (つづき)

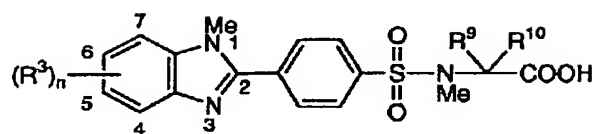


番号	(R ³) _n —	R ⁹ R ¹⁰	番号	(R ³) _n —	R ⁹ R ¹⁰
1 1	6-CH ₃		1 6	5,6-diCH ₃	
1 2	6-CH ₃		1 7	5,6-diCH ₃	
1 3	6-CH ₃		1 8	5,6-diCH ₃	
1 4	6-CH ₃		1 9	5,6-diCH ₃	
1 5	6-CH ₃		2 0	5,6-diCH ₃	

[0122]

[Table 93]

表 3 1 (つづき)

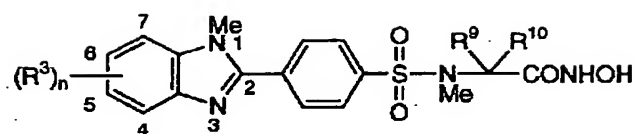


番号	(R ³) _n —	$\begin{array}{c} \text{R}^9 \quad \text{R}^{10} \\ \diagdown \quad \diagup \\ \text{---} \end{array}$	番号	(R ³) _n —	$\begin{array}{c} \text{R}^9 \quad \text{R}^{10} \\ \diagdown \quad \diagup \\ \text{---} \end{array}$
2 1	5-OCH ₃		2 6	6-OCH ₃	
2 2	5-OCH ₃		2 7	6-OCH ₃	
2 3	5-OCH ₃		2 8	6-OCH ₃	
2 4	5-OCH ₃		2 9	6-OCH ₃	
2 5	5-OCH ₃		3 0	6-OCH ₃	

[0123]

[Table 94]

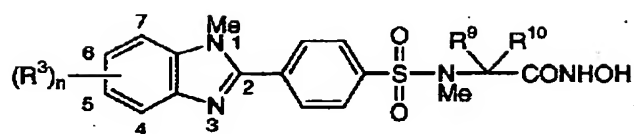
表 3 2



番号	(R ³) _n —	R ⁹ R ¹⁰	番号	(R ³) _n —	R ⁹ R ¹⁰
1	H		6	5-CH ₃	
2	H		7	5-CH ₃	
3	H		8	5-CH ₃	
4	H		9	5-CH ₃	
5	H		10	5-CH ₃	

[0124]
[Table 95]

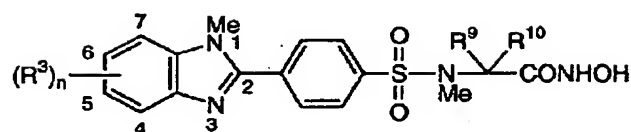
表 3 2 (つづき)



番号	(R ³) _n —	$\begin{array}{c} \text{R}^9 \quad \text{R}^{10} \\ \diagdown \quad \diagup \\ \text{C} \end{array}$	番号	(R ³) _n —	$\begin{array}{c} \text{R}^9 \quad \text{R}^{10} \\ \diagdown \quad \diagup \\ \text{C} \end{array}$
1 1	6-CH ₃		1 6	5,6-diCH ₃	
1 2	6-CH ₃		1 7	5,6-diCH ₃	
1 3	6-CH ₃		1 8	5,6-diCH ₃	
1 4	6-CH ₃		1 9	5,6-diCH ₃	
1 5	6-CH ₃		2 0	5,6-diCH ₃	

[0125]
[Table 96]

表3 2 (つづき)



番号	(R ³) _n —	R ⁹ R ¹⁰	番号	(R ³) _n —	R ⁹ R ¹⁰
2 1	5-OCH ₃		2 6	6-OCH ₃	
2 2	5-OCH ₃		2 7	6-OCH ₃	
2 3	5-OCH ₃		2 8	6-OCH ₃	
2 4	5-OCH ₃		2 9	6-OCH ₃	
2 5	5-OCH ₃		3 0	6-OCH ₃	

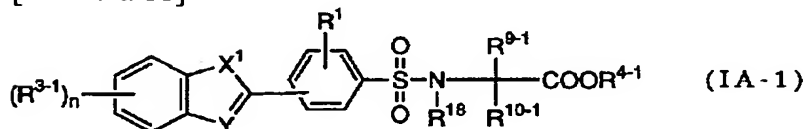
[0126]

[Methods for Producing the Invented Chemical Compound]this invention compound shown by general formula (I) can be manufactured by the method indicated in the following methods or examples.

(1) R² can manufacture the compound which is COOR⁴ by the method of of the following (a) or (b) among this invention compounds shown by general formula (I).

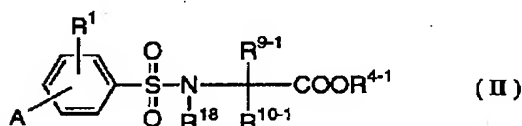
(a) Neither R³ nor R⁹ nor R¹⁰ group nor the COOR⁴ group in R² expresses the basis containing - COOH group or it, And the thing [any] group of R³, R⁹, and R¹⁰ group does not express the basis containing a hydroxyl group or it, (And the compound in which the thing [any] group of R³, X, R⁹, and R¹⁰ group does not express the basis containing an amino group or it, i.e., a general formula, (IA-1))

[Formula 11]



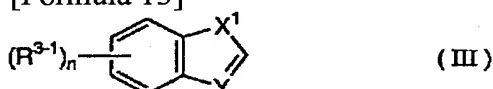
the inside of a formula, and R⁴⁻¹ -- C1 - 8 alkyl groups, a phenyl group, or a phenyl group. - An OCOR⁶ group (R⁶ expresses the same meaning as the above among a basis.), or a -CONR⁷R⁸ group (among a basis) R⁷ and R⁸ express the same meaning as the above. C1 replaced - 4 alkyl groups are expressed. Although it expresses and X¹

expresses the same meaning as X, Although the amino group in X^1 expresses the protected amino group and R^{3-1} , R^{9-1} , and R^{10-1} express the respectively same meaning as R^3 , R^9 , and R^{10} , The inside of R^{3-1} , R^{9-1} , and R^{10-1} group, - COOH group, The basis containing a hydroxyl group, an amino group, or them expresses the basis containing the protected bases or those bases that were protected, respectively, and other signs express the same meaning as the above. The compound shown is general formula (II). [Formula 12]



(A expresses a halogen atom or a trifluoromethane sulfonyloxy group among a formula, and other signs express the same meaning as the above.) -- the compound shown and general formula (III)

[Formula 13]

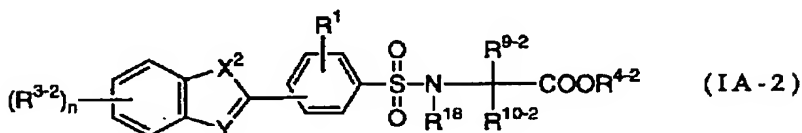


(all the signs express the same meaning as the above among a formula.) -- it can manufacture by making the compound shown react.

[0127]The reaction with the condensed heterocyclic compound shown by the compound shown by general formula (II) and general formula (III) is publicly known, for example, the inside (tetrahydrofuran etc.) of an organic solvent and alkyl lithium (n-butyl lithium.) Under existence of halogenation metal (zinc chloride, a magnesium chloride, or trialkyltin chloride (trimethyl tin chloride)), such as t-butyl lithium, It can manufacture by making it react at 0-100 ** using catalysts (tetrakis (triphenyl phosphine) palladium etc.).

[0128](b) The basis of either R^3 , R^9 , R^{10} group and the $COOR^4$ group in R^2 . [whether the basis containing - COOH group or it is expressed, and] Or the basis of either R^3 , R^9 and R^{10} group. [whether the basis containing a hydroxyl group or it is expressed, and] (Or the compound showing the basis on which the basis of either R^3 , X , R^9 and R^{10} group contains an amino group or it, i.e., a general formula, (IA-2))

[Formula 14]



(Among a formula, although the respectively same meaning as R^3 , X , R^4 , R^9 , and R^{10} is expressed, R^{3-2} , X^2 , R^{4-2} , R^{9-2} , and R^{10-2}) At least one basis among R^{3-2} , X^2 , a $COOR^{4-2}$ group, R^{9-2} , and R^{10-2} - COOH group, Expressing the basis containing a hydroxyl group, an amino group, or them, other signs express the same meaning as the above. The compound shown can be manufactured by giving the compound shown by a general formula (IA-1) to the deprotection reaction under alkali hydrolysis or acid conditions.

[0129]a deprotection reaction by alkali hydrolysis is publicly known -- for example, an organic solvent (methanol.) hydroxide (sodium hydroxide.) of inside and alkaline

metals, such as a tetrahydrofuran and dioxane A potassium hydrate, lithium hydroxide, etc. are performed at temperature of 0-40 ** using hydroxide (calcium hydroxide etc.), carbonate (sodium carbonate, potassium carbonate, etc.), solution of those, or these mixtures of alkaline-earth metals. a deprotection reaction under acid conditions is also publicly known -- for example, an organic solvent (a methylene chloride.) It is carried out at temperature of 0-90 ** into chloroform, dioxane, ethyl acetate, an anisole, etc. among organic acid (trifluoroacetic acid, methanesulfonic acid, iodination trimethylsilyl, etc.), inorganic acid (chloride etc.), or these mixtures (hydrogen bromide acetic acid etc.).

[0130]An ester compound which carries out considerable can be manufactured by giving a compound which has at least one - COOH group among compounds shown by a general formula (IA-2) to an esterification reaction. An esterification reaction is publicly known, for example, a method of using (1) diazoalkane, a method of using (2) alkyl halide, a method of using a (3) dimethylformamide (DMF)-dialkyl acetal, a method of making it react to alkanol (4) Corresponding, etc. are mentioned.

[0131]If these methods are explained concretely, the method of using (1) diazoalkane, For example, it is carried out by making it react at -10 **-40 ** using corresponding diazoalkane among an organic solvent (diethylether, ethyl acetate, a methylene chloride, acetone, methanol, ethanol, etc.).

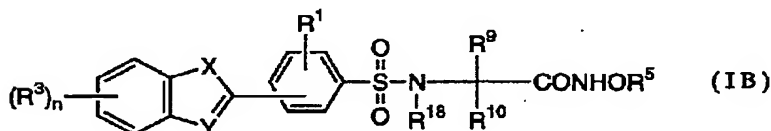
(2) the method of using alkyl halide -- an organic solvent (acetone.) It is carried out into DMF, dimethyl sulfoxide (DMSO), etc. using corresponding alkyl halide by making it react at -10 ** - 40 ** under existence of bases (potassium carbonate, sodium carbonate, potassium bicarbonate, sodium bicarbonate, a calcium oxide, etc.).

(3) The method of using a DMF-dialkyl acetal is performed, for example among an organic solvent (benzene, toluene, etc.) using a corresponding DMF-dialkyl acetal by making it react at -10 ** - 40 **.

(4) The method of making it react to corresponding alkanol, for example, the inside of corresponding alkanol and acid (chloride, sulfuric acid, and p-toluenesulfonic acid.) It is carried out by making it react at 0-40 ** using condensing agents (1,3-dicyclohexylcarbodiimide (DCC), pivaloyl halide, aryl sulfonyl halide, alkyl sulfonyl halide, etc.), such as hydrogen chloride gas. Of course, these esterification reactions may add the organic solvents (a tetrahydrofuran, a methylene chloride, etc.) which do not participate in a reaction, and may be performed.

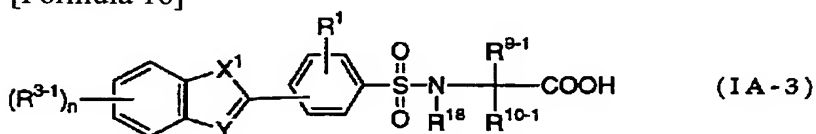
[0132]((2) The compound (IB), i.e., the general formula, whose R² is CONHOR⁵ among this invention compounds shown by general formula (I))

[Formula 15]



(all the signs express the same meaning as the above among a formula.) -- the compound shown -- general formula (IA-3)

[Formula 16]



(all the signs express the same meaning as the above among a formula.) -- the compound shown and general formula (IV)

[Formula 17] $\text{NH}_2\text{OR}^{5-1}$ (IV)

the inside of a formula, and R^{5-1} -- a hydrogen atom, C1 - 8 alkyl groups, and a phenyl group. Or C1 replaced by the phenyl group - 4 alkyl groups, or the protective group of the other hydroxylamine. (For example, $-\text{C}(\text{CH}_3)_2\text{OCH}_3$, a t-butoxycarbonyl group, or a benzyloxycarbonyl group) etc. is expressed. It can manufacture by giving an amidation reaction with the compound shown. If required, it can also manufacture by giving the hydrolysis under alkali conditions, and/or the deprotection reaction under acid conditions succeedingly.

[0133] The amidation reaction in which make amine react to acid and an amide bond is made to form is publicly known, for example, the method of using (1) acid halide, the method of using (2) mixed acid anhydrides, the method of using (3) condensing agents, etc. are mentioned.

[0134] If these methods are explained concretely, the method of using (1) acid halide, For example, carboxylic acid with the inside (chloroform, a methylene chloride, diethylether, a tetrahydrofuran, etc.) of an organic solvent, or a non-solvent. It is made to react to acid halide (oxalyl chloride, thionyl chloride, etc.) at -20°C - flowing-back temperature, It is carried out by making the obtained acid halide react to amine at $0-40^\circ\text{C}$ among an organic solvent (chloroform, a methylene chloride, diethylether, a tetrahydrofuran, etc.) under existence of the third class amine (pyridine, triethylamine, dimethylaniline, dimethylamino pyridine, etc.).

[0135] (2) The methods of using a mixed acid anhydride are inside (chloroform, a methylene chloride, diethylether, a tetrahydrofuran, etc.) of an organic solvent, or a non-solvent about carboxylic acid, for example, Under existence of the third class amine (pyridine, triethylamine, dimethylaniline, dimethylamino pyridine, etc.), Acid halide (a pivaloyl chloride, tosyl chloride, mesyl chloride, etc.). Or it is carried out by making it react to acid derivatives (ethyl chloroformate, KUROROGI acid isobutyl, etc.) at $0-40^\circ\text{C}$, and making the mixed acid anhydride and amine which were obtained react at $0-40^\circ\text{C}$ among an organic solvent (chloroform, a methylene chloride, diethylether, a tetrahydrofuran, etc.).

[0136] (3) The method of using a condensing agent is a non-solvent about carboxylic acid and amine, for example among an organic solvent (chloroform, a methylene chloride, dimethylformamide, diethylether, a tetrahydrofuran, etc.), Under existence of the third class amine (pyridine, triethylamine, dimethylaniline, dimethylamino pyridine, etc.) or nonexistence, a condensing agent (1,3-dicyclohexylcarbodiimide (DCC) and 1-ethyl-3-[3-(dimethylamino) propyl] carbodiimide (EDC).) It is carried out by making it react at $0-40^\circ\text{C}$ without using whether 1-hydroxybenzotriazole (HOBt) is used using 1,1'-carbonyldiimidazole (CDI), 2-chloro-1-methylpyridinium iodine, etc. As for each of reactions of these (1), (2), and (3), it is desirable under inactive gas (argon, nitrogen, etc.) atmosphere to carry out on anhydrous conditions.

[0137] A deprotection reaction means the deprotection reaction under the general deprotection reaction which a person skilled in the art can understand easily, for example, alkali hydrolysis, and acid conditions, and this invention compound made into the purpose is easily manufactured by using these reactions properly.

Deprotection under alkali hydrolysis and acid conditions can be performed by the same method as the above.

[0138] Although it is that a person skilled in the art can understand easily, and t-butyl group and benzyl are mentioned as a protective group of a carboxyl group and a

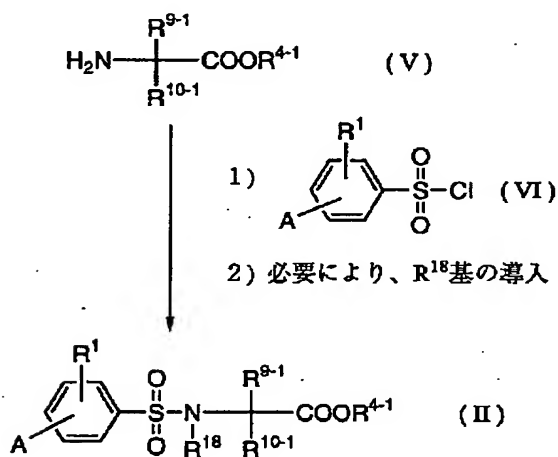
hydroxyl group, it will not be limited especially if it is a basis from which it can be desorbed easily and selectively besides it. For example What was indicated to T. W. Greene, Protective Groups in Organic Synthesis, Wiley, New York, and 1991 is used. As a protective group of an amino group, although a benzyloxycarbonyl group and a t-butoxycarbonyl group are mentioned, especially if it is a basis from which it can be desorbed easily and selectively besides it, it will not be limited. For example, $-\text{C}(\text{CH}_3)_2\text{OCH}_3$ etc. are used. this invention compound made into the purpose is easily manufactured by using these protective groups properly. It will not be limited especially if it is a basis from which it can be desorbed easily and selectively besides t-butyl group and benzyl as a protective group of hydroxylamine. For example, $-\text{C}(\text{CH}_3)_2\text{OCH}_3$, a t-butoxycarbonyl group, or a benzyloxycarbonyl group is used. this invention compound made into the purpose is easily manufactured by using these protective groups properly.

[0139] The compound shown by general formula (II) can be manufactured by the method shown by the publicly known method or the following reaction process type 1. A series of reactions are shown in the following reaction process types 2 and 3.

[0140]

[Formula 18]

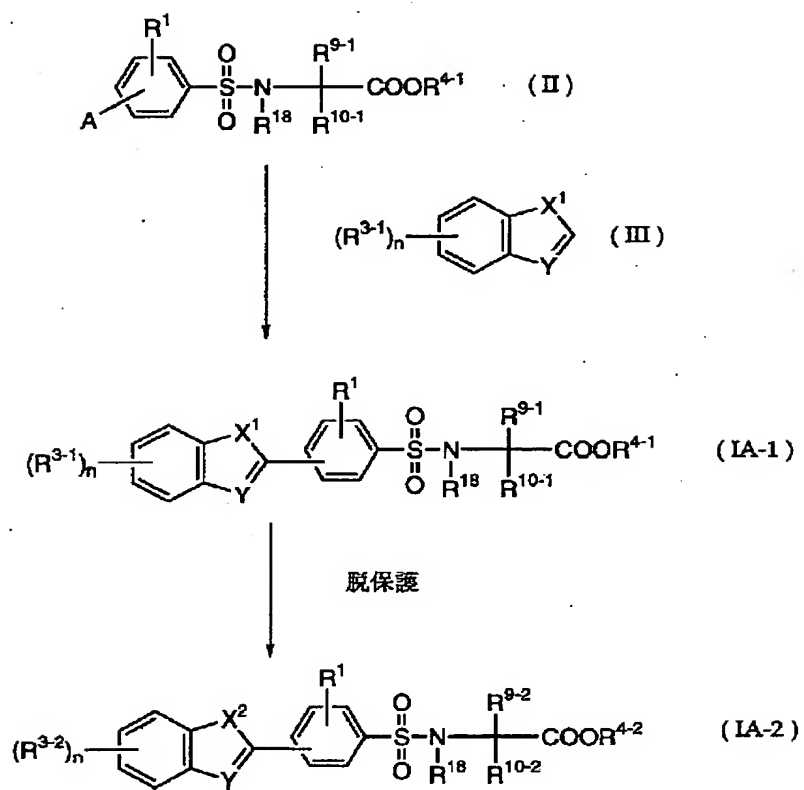
反応工程式 1



[0141]

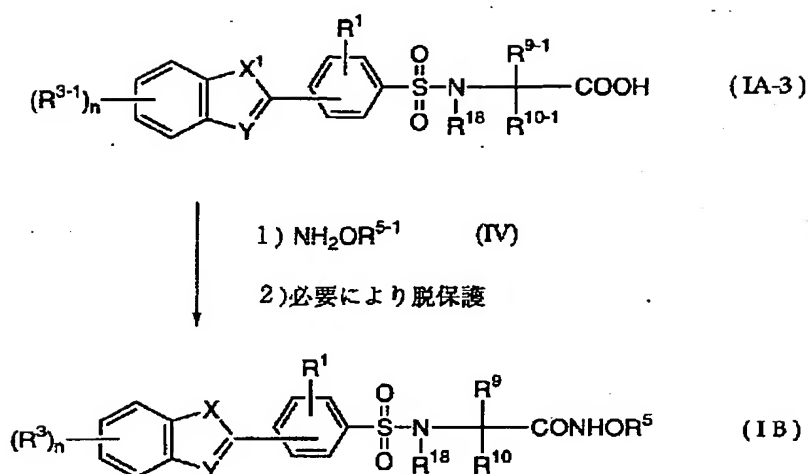
[Formula 19]

反应工程式 2



[0142]
[Formula 20]

反応工程式 3



[0143]The compound shown by general formula (IV), general formula (V), or general formula (VI) used as a starting material is publicly known in itself, or can be easily manufactured by a publicly known method. Other starting material and each reagent (for example, compound shown by general formula (III)) in this invention are publicly known in itself, or can be manufactured by a publicly known method.

[0144]In each reaction in this specification, a refining means usual in a resultant. For example, it can refine by methods using distillation under ordinary pressure or decompression, silica gel, or a magnesium silicate, such as high performance chromatography, thin layer chromatography, column chromatography or washing, and recrystallization. Refining may be performed for every reaction and it may carry out after some ending reaction.

[0145]

[Pharmacological activity] The following experiments proved that this invention compound shown by general formula (I) has matrix metalaw proteinase inhibiting activity.

[0146](1) an assay buffer (90microl) solution of the pro gelatinase A (7microl) refined from a gelatinase A inhibiting activity [experimental method] Homo sapiens normal dermal fibroblast (HNDf) -- p-aminophenyl mercury acetate (APMA) (10microl) of 10mM -- in addition, Preincubation was carried out at 37 ** for 1 hour, and an enzyme was activated. A solution (10microl) which does not add a solution of a test compound or a test compound of a synthetic substrate (MOCAC-Pro-Leu-Gly-A₂pr(Dnp)-Ala-Arg-NH₂) (890microl; last concentration 13.5microM) and various concentration. Preincubation was carried out for 5 minutes at 37 **, activating enzyme (7microl/tube, 100microl) prepared above there -- in addition, the incubation was carried out for 20 minutes at 37 **, after that, a 0.1M sodium acetate buffer (2ml;pH4.0) was added, and an enzyme reaction was stopped. Gelatinase activity was computed by measuring fluorescence intensity (Ex=328nm and Em = 393 nm) of a reaction solution. A result is shown in Table 33.

[0147]

[Table 97]

表 3 3

实施例番号	I C ₅₀ (μ M)
2	1. 8
2 (4)	1. 6
2 (6)	7. 4
2 (8)	1. 1
3	0. 3 0

[0148](2) the assay buffer (105microl) solution of pro collagenase (5microl) refined from the collagenase inhibiting activity [experimental method] Homo sapiens normal dermal fibroblast (HNDF) -- 1mg/ml of trypsin (45microl) -- in addition, Preincubation was carried out for 1 minute at 37 **, and the enzyme was activated. 5mg/ml soybean trypsin inhibitor (soybean trypsin inhibitor) (SBTI;50microl) was added in the solution, and inactivation of the trypsin was carried out to it. The solution of a test compound or test compound of a synthetic substrate (Ac-Pro-Leu-Gly-[2-mercapto-4-methyl-pentanoyl]-Leu-Gly-OEt) (105microl; last concentration 1.33mM) and various concentration. Preincubation of the solution (20microl) which is not added was carried out for 5 minutes at 26 **. the activating enzyme (75microl/tube, 50microl) prepared above there -- in addition, the incubation was carried out for 10 minutes at 26 **. The absorbance of 324 nm of a total of 40 points was measured in these 10 minutes, and Vmax in 30 points of them was made into measured value. For example, the compound of Example 2 (1) checked collagenase activity 69.3% by the concentration of 100mM.

[0149]

[Toxicity] It can be judged that the toxicity of this invention compound is very low, and it is safe enough in order to use it as medicine.

[0150]

[Application in drugs] In an animal including Homo sapiens, especially Homo sapiens, by checking matrix metalaw proteinase, for example, gelatinase, SUTOROMU lysin, or collagenase. Rheumatism, osteoarthritis, morbid osteoclasia, osteoporosis, periodontosis, the interstitial nephritis, It is useful for prevention and/or the therapy of the disease of arteriosclerosis, versicular emphysema, liver cirrhosis, cornea damage, transition permeation of a cancer cell, or growth, an autoimmune disease, the diseases (Crohn's disease, a SHUGUREN disease, etc.) by the blood vessel transmigration of the cell of a leucocyte system, or permeation, the vascularization, etc.

[0151]In order to use this invention compound shown by general formula (I), its nontoxic salt, acid addition salt, or its hydrate for the above-mentioned purpose, a medicine is usually prescribed for the patient in taking orally or a parenteral form systemic or locally. Although a dose changes with age, weight, condition, a curative effect, a medication method, processing time, etc., Usually, in 1 to [per time per one adult] 1000 mg, It is administered orally several times from 1 time per day, parenteral administration (it administers intravenously preferably) is carried out several times from 1 time per day in 1 to [per time per one adult] 100 mg, or self-sustaining

administration is carried out into a vein in 1 to [per] 24 hours day. As described above, of course, since a dose is changed by various conditions, a quantity smaller than the above-mentioned dose may be enough as it, and it may be required exceeding the range.

[0152]When prescribing this invention compound for the patient, it is used as the injections for the solid constituent for internal use, a liquid composition, other constituents, and parenteral administration, external preparations, suppositories, etc. A tablet, a pill, a capsule, powder medicine, a granule, etc. are contained in the solid constituent for internal use. A hard capsule and a soft capsule are contained in a capsule. In such a solid constituent, one or the active substance beyond it, It is mixed with one inertness diluent, for example, lactose, mannitol, glucose, hydroxypropylcellulose, microcrystalline cellulose, starch, a polyvinyl pyrrolidone, and magnesium aluminometasilicate at least. The constituent may contain a solubilizing agent like additive agents other than an inertness diluent, for example, lubricant like magnesium stearate, disintegrator like a calcium carboxymethyl cellulose, a stabilizing agent like lactose, glutamic acid, or aspartic acid in accordance with a conventional method. The tablet or the pill may be covered with the film of stomach solubility, such as white soft sugar, gelatin, hydroxypropylcellulose, and hydroxypropylmethylcellulose phthalate, or an enteric substance as occasion demands, and may be covered with two or more layers. The capsule of a substance still like gelatin by which it is absorbed and in which it deals is also included.

[0153]The liquid composition for internal use contains an opacifier, a solution agent, syrups, elixirs, etc. which are permitted in drugs. In such a liquid composition, one or the active substance beyond it contains in the inertness diluent (for example, purified water, ethanol) generally used. This constituent may contain a wetting agent, an adjuvant like suspension, the sweetening agent, the flavor agent, the aromatic, and the antiseptic in addition to an inertness diluent. As a constituent of others for internal use, the spray prescribed by a publicly known method in itself is contained including one or the active substance beyond it. This constituent may contain an isotonic agent like a buffer which gives stabilizer and the isotonicity like sodium hydrogen sulfite in addition to an inertness diluent, for example, sodium chloride, sodium acid citrate, or citrate. The manufacturing method of spray is *****, for example. 2,868,691 It is indicated in detail in an item and the 3,095,355th item.

[0154]As injections for the parenteral administration by this invention, a sterile water or non-aqueous solution agent, suspension, and an opacifier are included. As a water solution agent and suspension, distilled water for injection and a physiological saline are contained, for example. As the solution agent of nonaqueous solubility, and suspension, there are propylene glycol, a polyethylene glycol, vegetable oil like olive oil, alcohols like ethanol, polysorbate 80 (registered trademark), etc., for example. Such a constituent may contain an adjuvant still like an antiseptic, a wetting agent, an emulsifier, a dispersing agent, a stabilizing agent (for example, lactose), and a solubilizing agent (for example, glutamic acid, aspartic acid). These are sanitized by the combination or the exposure of filtration and a germicide which lets a bacteria suspension filter pass. These manufacture a sterile solid constituent again, for example, they can also use it for sanitization, sterile distilled water for injection, or other solvents before use of a freeze-drying article, dissolving. As a constituent of others for parenteral administration, the pessary for the suppositories for the outside solution agent prescribed by a conventional method, ointment, the paint, and intrarectal administration and the administration in a vagina, etc. are contained including one or the active substance beyond it.

[Translation done.]

* NOTICES *

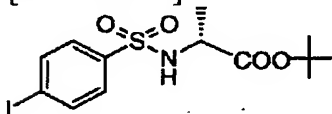
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1. This document has been translated by computer. So the translation may not reflect the original precisely.
2. **** shows the word which can not be translated.
3. In the drawings, any words are not translated.

EXAMPLE

[Example] Hereafter, although this invention is explained in full detail according to a reference example and an example, this invention is not limited to these. The solvent in the parenthesis shown in the part and TLC of separation by chromatography shows the used elution solvent or developing solvent, and a rate expresses a volume ratio. The solvent in the parenthesis shown in the part of NMR shows the solvent used for measurement.

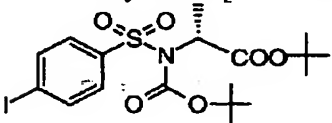
[0156] A reference example 1N-(4-iodo phenyl sulfonyl)-D-alanine and t-butylester [Formula 21]



[0157] 4-iodobenzene sulfonyl chloride (15.1g) was gradually added to the pyridine (100 ml) solution of D-alanine and t-butylester hydrochloride (9.08g) under ice-cooling. The mixture was removed from the ice bath and it agitated at the room temperature for 1 hour. The reaction solution was condensed, and it diluted with ethyl acetate, 1N chloride, water, and a saturation salt solution washed, and it condensed after desiccation with anhydrous magnesium sulfate. Silica gel chromatography (n-hexane: ethyl acetate = 3:1 → 2:1) refined residue, and the title compound (14.3g) which has the following property value was obtained.

TLC: R_f 0.65 (n-hexane: ethyl acetate = 1:1).

[0158] A reference example 2N-(4-iodo phenyl sulfonyl)-N-t-carbobutoxy-D-alanine and t-butylester [Formula 22]

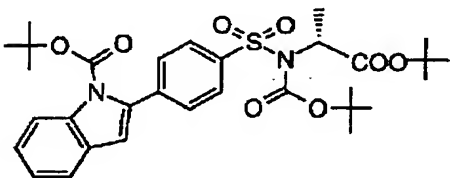


[0159] An N-(4-iodo phenyl sulfonyl)-D-alanine and t-butylester (it manufactured by the reference example 1.) (14g), It mixed at the room temperature and di-t-butyl dicarbonate (8g), 4-(dimethylamino) pyridine (50 mg), and acetonitrile (34 ml) were agitated for 1 hour. The reaction mixture was condensed, silica gel chromatography (n-hexane: ethyl acetate = 10:1) refined residue, and the title

compound (17.1g) which has the following property value was obtained.

TLC:Rf 0.39 (n-hexane: ethyl acetate =5:1).

[0160]An example 1N--[4-(1-t-butoxy KARUBONI *-*****- 2-yl) phenyl slufonyl]] N-t-carbobutoxy-D-alanine and t-butylester [Formula 23]

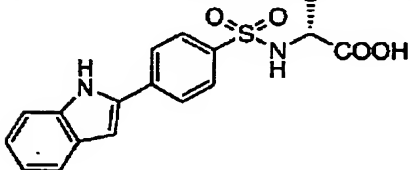


[0161]The pentane (8.8 ml) solution of t-butyl lithium of 1.5M was dropped at the tetrahydrofuran (20 ml) solution of N-t-butoxycarbo NIRUINDORU (2.61g) during the dry ice methanol bath, and was agitated for 1 hour. The diethylether (13.2 ml) solution of zinc chloride of 1M was dropped at the mixture during the dry ice methanol bath. It is neglected until it removes reaction mixed liquor from a dry ice methanol bath and becomes 0 **, One by one, an N-(4-iodo phenyl slufonyl)-N-t-carbobutoxy-D-alanine, t-butylester (it manufactured by the reference example 2.) (2.05g), and tetrakis (triphenyl phosphine) palladium (462 mg) were added at 0 **, and were agitated at the room temperature for 1 hour. Reaction mixed liquor was diluted with ethyl acetate, 1N chloride and saturated sodium bicarbonate solution washed, and it condensed after desiccation with anhydrous magnesium sulfate. Silica gel chromatography (n-hexane: ethyl acetate =10:1->5:1) refined residue, and the title compound (2.36g) which has the following property value was obtained.

[0162]TLC:Rf 0.34 (n-hexane: ethyl acetate =5:1);

NMR. (CD₃OD) :. delta 8.21-8.17(1H,m), 8.04(2H,d,J=8.7Hz), 7.60-7.56(1H,m), 7.57(2H,d,J=8.7Hz), 7.42-7.21(3H,m), 5.11(1H,q, J= 7.0 Hz, 1.66 (3H,d,J=7.0Hz), 1.46 (9H, s), 1.38 (18H, s).

[0163]Example 2N-[4-(2-indolyl) phenyl slufonyl]-D-alanine [Formula 24]



[0164]An N--[4-(1-t-butoxy KARUBONI *-*****- 2-yl) phenyl slufonyl]] N-t-carbobutoxy-D-alanine and t-butylester (it manufactured in Example 1.) (2.3g) were dissolved in trifluoroacetic acid (10 ml), and it agitated for 30 minutes at the room temperature. Diisopropyl ether washed the solid obtained by distilling off trifluoroacetic acid, it dried and the title compound (1.07g) which has the following property value was obtained.

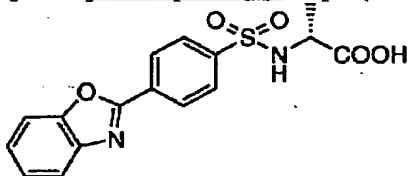
[0165]TLC:Rf 0.18 (chloroform: methanol : acetic acid =10:1:1);

NMR. (CD₃OD) :. delta 7.94(2H,d,J=8.8Hz), 7.88(2H,d,J=8.8Hz), 7.56(1H,br.d,J=7.8Hz), 7.41(1H,br.d,J=8.0Hz), 7.14(1H,td,J=7.8, 1.2 Hz, 7.02 (1H, ddd, J= 8.0, 7.8, 1.2 Hz), 6.97 (1H, br.s), 3.94 (1H, q, J= 7.2 Hz), 1.33 (3H, d; J= 7.2 Hz).

[0166]Amino acid and t-butylester (hydrochloride) corresponding by the example 2(1)-2 (19) reference example 1 instead of D-alanine and t-butylester hydrochloride are used, The compound manufactured by the compound or the reference example 2 produced by operating it like the method shown by the reference example 1 ->

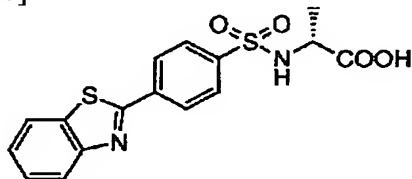
reference example 2 is used, The title compound which operates it like the method shown in example 1 (heterocyclic compound corresponding instead of N-t-butoxycarbo NIRUINDORU was used.) -> example 2, and has the following property value was obtained.

[0167] Example 2(1) N-[4-(2-benzoxazolyl) phenyl slufonyl]-D-alanine [Formula 25]



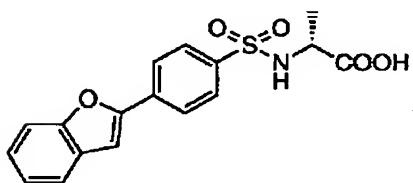
[0168] TLC:Rf 0.20 (methanol: chloroform : acetic acid : water =100:10:1:1);
NMR. (CD₃OD) :delta J= 7.1 Hz of 8.55(2H,d,J=8.6Hz), 8.05(2H,d,J=8.6Hz), 7.8-7.7(2H,m), 7.5-7.4(2H,m), 4.01(1H,q,J=7.1Hz), 1.36(3H,d,).

[0169] Example 2(2) N-[4-(2-benzothiazolyl) phenyl slufonyl]-D-alanine [Formula 26]



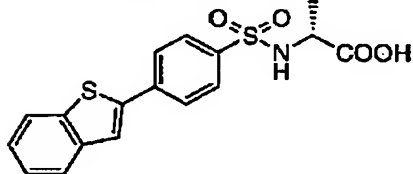
[0170] TLC:Rf 0.22 (methanol: chloroform : acetic acid : water =100:10:1:1);
NMR(CD₃OD): delta 8.26 (2H, d, J= 8.3 Hz), 8.1-8.0 (4H, m), 7.6-7.45 (2H, m), 4.00 (1H, q, J= 7.3 Hz), 1.36 (3H, d, J= 7.3 Hz).

[0171] Example 2(3) N-[4-(2-benzofuranyl) phenyl slufonyl]-D-alanine [Formula 27]



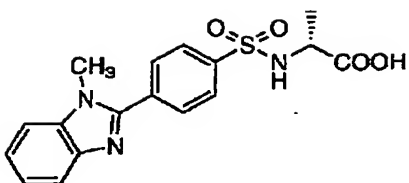
[0172] TLC:Rf 0.23 (chloroform: methanol : acetic acid =30:1:1);
NMR. (CD₃OD) :delta 8.05(2H,d,J=8.8Hz), 7.93(2H,d,J=8.8Hz), 7.67-7.53(2H,m), 7.37(1H,s), 7.38-7.21(2H,m), 3.96(1H,q,J=7.2Hz), 1.34 (3H, d, J= 7.2 Hz).

[0173] Example 2(4) N-[4-(2-benzo thienyl) phenyl slufonyl]-D-alanine [Formula 28]



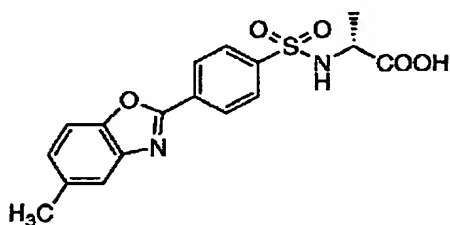
[0174] TLC:Rf 0.27 (chloroform: methanol : acetic acid =30:1:1);
NMR. (DMSO-d₆) :delta 13.20-11.87(1H,br), 8.32-8.18(1H,m), 8.05-7.85(7H,m), 7.47-7.37(2H,m), 3.88-3.76(1H,m), 1.20(3H,d,J=7.0Hz).

[0175] Example 2(5) N-[4-(1-methylbenzimidazol 2-yl) phenyl slufonyl]-D-alanine [Formula 29]



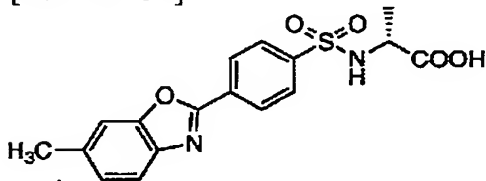
[0176]TLC:Rf 0.41 (methanol: chloroform : acetic acid : water =50:10:1:1);
NMR. (DMSO- d_6) δ : 8.43(1H,d,J=8.2Hz), 8.10(2H,d,J=8.6Hz),
8.03(2H,d,J=8.6Hz), 7.83(2H,m), 7.50(2H,m), 3.98(3H,s), 3.89 (1H, m), 1.11 (3H, d,
J= 7.3 Hz).

[0177]Example 2(6) N-[4-(5-methylbenzoxazol- 2-yl) phenyl slufonyl]-D-alanine
[Formula 30]



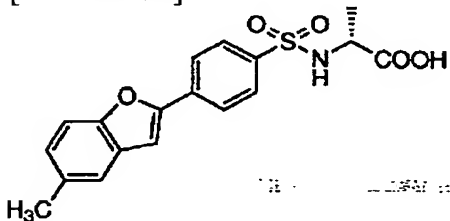
[0178]TLC:Rf 0.43 (methanol: chloroform : acetic acid : water =50:10:1:1);
NMR. (DMSO- d_6) δ : 12.78(1H,brs), 8.38(1H,d,J=8.6Hz), 8.33(2H,d,J=8.8Hz),
7.97(2H,d,J=8.8Hz), 7.68(1H,d,J=8.3Hz), 7.63 (1H, d, J= 1.2 Hz), 7.27 (1H, dd, J=
1.2, 8.3 Hz), 3.85 (1H, dq, J= 8.6, 7.3 Hz), 2.45 (3H, s), 1.19 (3H,d,J=7.3Hz).

[0179]Example 2(7) N-[4-(6-methylbenzoxazol- 2-yl) phenyl slufonyl]-D-alanine
[Formula 31]



[0180]TLC:Rf 0.43 (methanol: chloroform : acetic acid : water =50:10:1:1);
NMR. (DMSO- d_6) δ : 12.76(1H,brs), 8.38(1H,d,J=8.8Hz), 8.31(2H,d,J=8.6Hz),
7.98(2H,d,J=8.6Hz), 7.72(1H,d,J=8.1Hz), 7.64 (1H, s), 7.23 (1H,d,J=8.1Hz), 3.83 (1H,
m), 2.48 (3H, s), 7.32 (3H,d,J=7.3Hz).

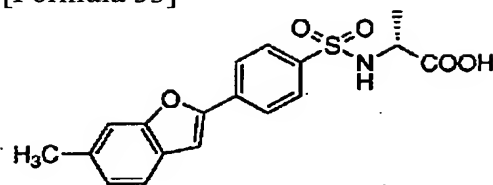
[0181]Example 2(8) N-[4-(5-methylbenzofuran-2-yl) phenyl slufonyl]-D-alanine
[Formula 32]



[0182]TLC:Rf 0.53 (chloroform: methanol : acetic acid =100:10:1);
NMR. (DMSO- d_6) δ : 8.23(1H,br.d,J=8.4Hz), 8.07(2H,d,J=8.4Hz),
7.87(2H,d,J=8.4Hz), 7.56(1H,s), 7.53(1H,d,J=8.4Hz), 7.48 (1H, br.s), 7.18
(1H,d,J=8.4), 3.89-3.74 (1H, m), 2.40 (3H, s), 1.17 (3H,d,J=6.8Hz).

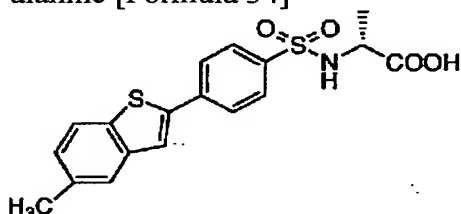
[0183]Example 2(9) N-[4-(6-methylbenzofuran-2-yl) phenyl slufonyl]-D-alanine

[Formula 33]



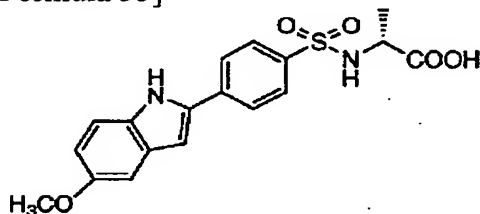
[0184]TLC:Rf 0.40 (chloroform: methanol : acetic acid =100:10:1);
NMR. (DMSO-d₆) :. delta 8.30-8.16(1H,m), 8.05(2H,d,J=8.4Hz), 7.86(2H,d,J=8.4Hz), 7.57(1H,br.s), 7.57(1H,d,J=8.0Hz), 7.47(1H,br.s), 7.12 (1H, br.d, J= 8.0 Hz), 3.89-3.71 (1H, m), 2.44 (3H, s), 1.17 (3H,d,J=7.2Hz).

[0185]Example 2 (10) N-[4-(5-methyl benzothiophene 2-yl) phenyl sulfonyl]-D-alanine [Formula 34]



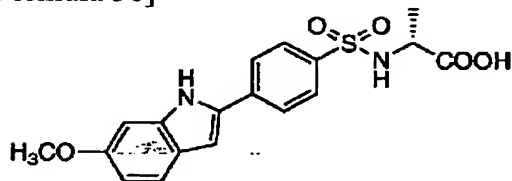
[0186]TLC:Rf 0.38 (chloroform: methanol : acetic acid =100:10:1);
NMR. (DMSO-d₆) :. delta 8.23(1H,br.d,J=8.4Hz), 7.96(1H,br.s), 7.95(2H,d,J=8.8Hz), 7.88(1H,d,J=8.8Hz), 7.84(2H,d,J=8.8Hz), 7.68 (1H, br.s), 7.23 (1H, dd, J= 8.2, 1.4 Hz), 3.88-3.73 (1H, m), 2.42 (3H, s), 1.18 (3H,d,J=7.0Hz).

[0187]Example 2 (11) N-[4-(5-methoxy indole- 2-yl) phenyl sulfonyl]-D-alanine [Formula 35]



[0188]TLC:Rf 0.34 (methanol: chloroform : acetic acid : water =50:10:1:1);
NMR. (CD₃OD) :.delta 7.91(2H,d,J=8.1Hz), 7.87(2H,d,J=8.1Hz), 7.18(1H,d,J=8.8Hz), 7.09(1H,d,J=2.6Hz), 6.80(1H,dd,J=2.6,8.8Hz), 3.92 (1H,q,J=7.3Hz), 3.81 (3H, s), 1.32 (3H, d).

[0189]Example 2 (12) N-[4-(6-methoxy indole- 2-yl) phenyl sulfonyl]-D-alanine [Formula 36]

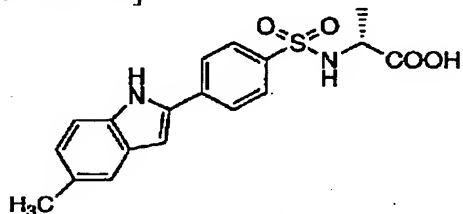


[0190]TLC:Rf 0.34 (methanol: chloroform : acetic acid : water =50:10:1:1);
NMR. (CD₃OD) :. delta 7.75(4H,s), 7.41(1H,d,J=8.8Hz), 6.92(1H,d,J=2.4Hz), 6.88(1H,d,J<1Hz), 6.69(1H,dd,J=2.4,8.8Hz), 3.92 (1H, q, J= 7.3 Hz), 3.83 (3H, s),

1.31 (3H, d, J= 7.3 Hz).

[0191] Example 2 (13) N-[4-(5-methylindole 2-yl) phenyl sulfonyl]-D-alanine

[Formula 37]

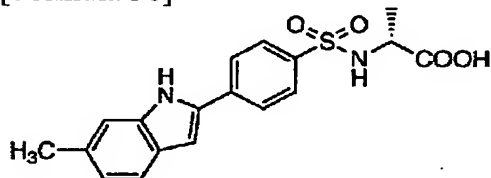


[0192] TLC: R_f 0.32 (methanol: chloroform : acetic acid : water =50:10:1:1);

NMR. (CD₃OD) : delta 7.89(2H,d,J=8.8Hz), 7.85(2H,d,J=8.8Hz), 7.32(1H,d,J=1.4Hz), 7.27(1H,d,J=8.3Hz), 6.97(1H,d,J=1.4,8.3Hz), 6.87 (1H,d,J<1Hz), 3.97 (1H,q,J=7.3Hz), 2.39 (3H, s), 1.32 (3H,d,J=7.3Hz).

[0193] Example 2 (14) N-[4-(6-methylindole 2-yl) phenyl sulfonyl]-D-alanine

[Formula 38]

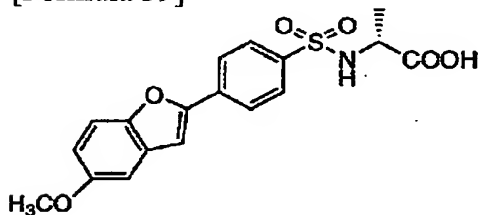


[0194] TLC: R_f 0.32 (methanol: chloroform : acetic acid : water =50:10:1:1);

NMR. (CD₃OD) : delta 7.89(2H,d,J=8.8Hz), 7.85(2H,d,J=8.8Hz), 7.42(1H,d,J=8.1Hz), 7.20(1H,d,J=1.2Hz), 6.90(1H,s), 6.89(1H, dd, J= 1.2, 8.1 Hz), 3.92 (1H,q,J=7.1Hz), 2.42 (3H, s), 1.32 (3H,d,J=7.1Hz).

[0195] Example 2 (15) N-[4-(5-methoxy benzofuran-2-yl) phenyl sulfonyl]-D-alanine

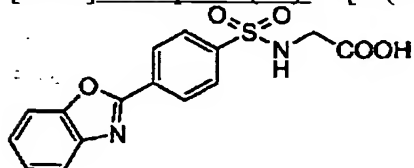
[Formula 39]



[0196] TLC: R_f 0.48 (methanol: chloroform : acetic acid : water =50:10:1:1);

NMR. (CD₃OD) : delta 7.98(2H,d,J=8.8Hz), 7.90(2H,d,J=8.8Hz), 7.41(1H,d,J=9.0Hz), 7.28(1H,s), 7.11(1H,d,J=2.4Hz), 6.91(1H, dd, J= 2.4, 9.0 Hz), 3.94 (1H,q,J=7.3Hz), 3.83 (3H, s), 1.32 (3H,d,J=7.3Hz).

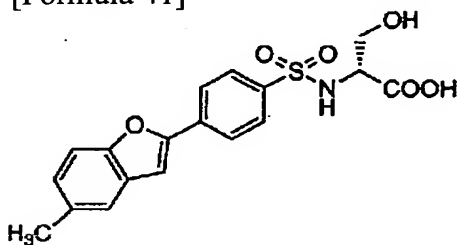
[0197] Example 2 (16) N-[4-(2-benzoxazolyl) phenyl sulfonyl] glycine [Formula 40]



[0198] TLC: R_f 0.30 (chloroform: methanol : acetic acid =85:15:1);

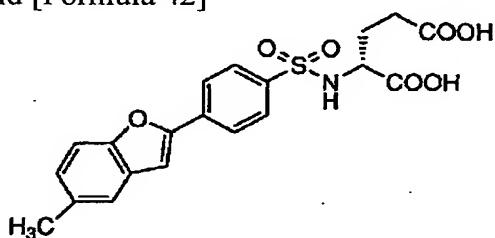
NMR. (DMSO-d₆) : delta 8.38(2H,d,J=8.8Hz), 8.30(1H,t,J=6.2Hz), 8.02(2H,d,J=8.8Hz), 7.92-7.80(2H,m), 7.52-7.43(2H,m), 3.67(2H, d, J= 6.2 Hz).

[0199] Example 2 (17) N-[4-(5-methyl-benzofuran-2-yl) phenyl sulfonyl]-D-serine
[Formula 41]



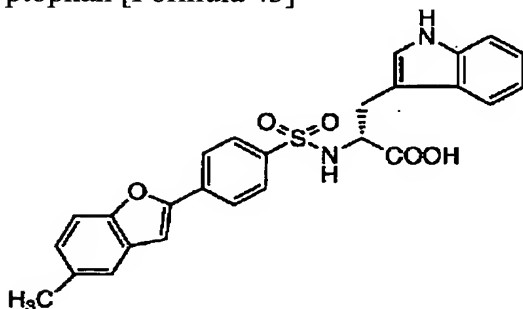
[0200] TLC: R_f 0.25 (chloroform: methanol : acetic acid =10:1:1);
NMR(DMSO-d₆): delta 8.12(1H,d,J=8.8Hz), 8.06(2H,d,J=8.8Hz), 7.88(2H,d,8.8Hz), 7.56(1H,s), 7.53(1H,d,J=8.6Hz), 7.48(1H,br.s), 7.18(1H,d,J=8.6,1.4Hz), 5.20-4.80(1H,br.), 3.81(1H,dt,J=8.8,5.2Hz), 3.52(2H,br.,J=5.2Hz), 2.40 (3H, s).

[0201] Example 2 (18) N-[4-(5-methyl-benzofuran-2-yl) phenyl sulfonyl]-D-glutamic acid [Formula 42]



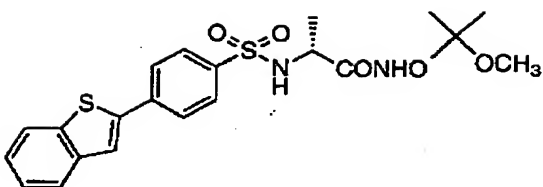
[0202] TLC: R_f 0.46 (chloroform: methanol : acetic acid =10:1:1);
NMR(DMSO-d₆): delta 12.80(2H,br.), 8.40-8.10(1H,br.), 8.06(2H,d,J=8.8Hz), 7.84(2H,d,J=8.8Hz), 7.55(1H,s), 7.53(1H,d,J=8.2Hz), 7.48(1H,br.s), 7.18(1H,dd,J=8.2Hz), 3.88-3.76(1H,m), 2.40(3H,s), 2.22(2H,t,J=7.0Hz), 1.95-1.57 (2H, m).

[0203] Example 2 (19) N-[4-(5-methyl-benzofuran-2-yl) phenyl sulfonyl]-D-tryptophan [Formula 43]



[0204] TLC: R_f 0.58 (chloroform: methanol : acetic acid =10:1:1);
NMR(DMSO-d₆): delta 10.78(1H,br.s), 7.85(2H,d,J=8.6Hz), 7.63(2H,d,J=8.6Hz), 7.54(1H,d,J=8.8Hz), 7.49(2H,br.s), 7.33-7.29 (1H,m), 7.22-7.15(2H,m), 7.07(1H,d,J=2.2Hz), 6.98-6.84(2H,m), 3.96-3.88(1H,m), 3.11-2.80(2H,m), 2.41 (3H, s).

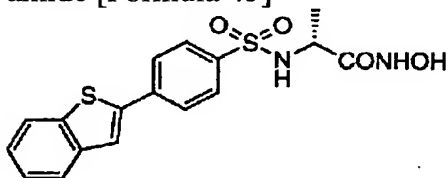
[0205] reference example 3 N-(1-methoxy-1,1'-dimethylmethoxy)- N'-[[4-(2-benzo thienyl) phenyl] sulfonyl]-D-alanyl] amide [Formula 44]



[0206] In the DMF (1 ml) solution of N-(1-methoxy-1,1-dimethylmethyloxy) amine (124 mg). An N-[4-(2-benzo thienyl) phenyl sulfonyl]-D-alanine (it manufactured in Example 2 (4).) (100 mg), HOBt-H₂O (42 mg), EDC-HCl (53 mg), and triethylamine (39 microl) were added under ice-cooling, and were agitated under the room temperature for 14 hours. Water was added after ending reaction and ethyl acetate extracted. The saturation salt solution washed the extract and it condensed after desiccation with anhydrous sodium sulfate. Ether washed the obtained crystal and the title compound (70 mg) which has the following property value was obtained.

TLC: R_f 0.17 (n-hexane: ethyl acetate = 2:1).

[0207] Example 3 N-hydroxy-N-[N'-[[4-(2-benzo thienyl) phenyl] Sulfonyl]-D-alanyl] amide [Formula 45]

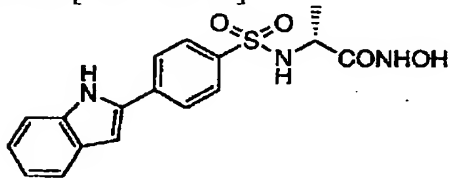


[0208] N-(1-methoxy-1,1-dimethylmethyloxy)- in the dioxane (3 ml) solution of N-[N'-[[4-(2-benzo thienyl) phenyl] sulfonyl]-D-alanyl] amide (it manufactured by the reference example 3.) (65 mg). 4N chloride-dioxane (0.2 ml) was added and it agitated for 30 minutes at the room temperature. Ether washed the crystal obtained by condensing after ending reaction, and the title compound (35 mg) which has the following property value was obtained.

TLC: R_f 0.46 (chloroform: methanol : acetic acid = 10:1:1);

NMR. (DMSO-d₆) : delta 10.59(1H, br.s), 8.84(1H, br.s), 8.14(1H, br.d, J=8.2Hz), 8.05-7.84(7H, m), 7.46-7.36(2H, m), 3.68-3.61(1H, m), 1.05 (3H, d, J= 7.4 Hz).

[0209] Example 3(1) N-hydroxy-N-[N'-[[4-(2-indolyl) phenyl]sulfonyl]-D-alanyl] amide [Formula 46]



[0210] The title compound which operates it like the method shown in reference example 3 -> example 3 using an N-[4-(2-indolyl) phenyl sulfonyl]-D-alanine (it manufactured in Example 2.), and has the following property value was obtained.

[0211] TLC: R_f 0.14 (methanol: chloroform : acetic acid : water = 100:10:1:1);

NMR(CD₃OD): delta 7.95 (2H, d, J= 8.8 Hz), 7.89 (2H, d, J= 8.8 Hz), 7.56 (1H, d, J= 7.7 Hz), 7.40 (1H, m), 7.14 (1H, m), 7.05 (1H, m), 6.98 (1H, d, J=2Hz), 3.77 (1H, q, J=7.0Hz), 1.21 (3H, d, J=7.0Hz).

[0212]

[Example(s) of Production]

It tableted, after mixing each one or less example [of pharmaceutical preparation]

ingredient with a conventional method, and 100 doses of tablets which contain a 50-mg active ingredient in 1 dose were obtained.

- N-[4-(2-benzo thienyl) phenyl slufonyl]-D-alanine 5.0 g and carboxymethyl-cellulose calcium (disintegrator) 0.2 g and magnesium stearate (lubricant) 0.1 g and microcrystalline cellulose 4.7 g[0213]After mixing each two or less example [of pharmaceutical preparation] ingredient with a conventional method, the solution was sterilized with the conventional method, and it filled up the ampul with 5 ml at a time, and freeze-dried with the conventional method, and 100 ampuls which contain a 20-mg active ingredient among 1 ampul were obtained.

- N-[4-(2-benzo thienyl) phenyl slufonyl]-D-alanine 2.0 g and mannitol 20g and distilled water 500 ml

[Translation done.]